Health Quality Subcommittee

Wednesday, January 11, 2017
9:00 AM – 11:00 AM
Mashburn Hall (306 HOB)

Richard Corcoran
Speaker

Cary Pigman
Chair

Committee Meeting Notice

HOUSE OF REPRESENTATIVES

Health Quality Subcommittee

Start Date and Time:	Wednesday, January 11, 2017 09:00 am
End Date and Time:	Wednesday, January 11, 2017 11:00 am
Location:	Mashburn Hall (306 HOB)
Duration:	2.00 hrs

Presentations and panel discussion on medical cannabis:

Christian Bax, Director of the Office of Compassionate Use, Florida Department of Health
Bertha Madras, PhD, Professor of Psychobiology, Harvard Medical School
Sue Sisley, MD, Scottsdale Research Institute LLC

NOTICE FINALIZED on 01/04/2017 4:13PM by Ellerkamp.Donna

Amendment 2

NO. 2 CONSTITUTIONAL AMENDMENT ARTICLE X, SECTION 29 (INITIATIVE)

Ballot Title: Use of Marijuana for Debilitating Medical Conditions

Ballot Summary:
Allows medical use of marijuana for individuals with debilitating medical conditions as determined by a licensed Florida physician. Allows caregivers to assist patients' medical use of marijuana. The Department of Health shall register and regulate centers that produce and distribute marijuana for medical purposes and shall issue identification cards to patients and caregivers. Applies only to Florida law. Does not immunize violations of federal law or any non-medical use, possession or production of marijuana.

Financial Impact Statement:
Increased costs from this amendment to state and local governments cannot be determined. There will be additional regulatory costs and enforcement activities associated with the production, sale, use and possession of medical marijuana. Fees may offset some of the regulatory costs. Sales tax will likely apply to most purchases, resulting in a substantial increase in state and local government revenues that cannot be determined precisely. The impact on property tax revenues cannot be determined.

Full Text:

ARTICLE X Miscellaneous

SECTION 29.– Medical marijuana production, possession and use.

(a) PUBLIC POLICY.

(1) The medical use of marijuana by a qualifying patient or caregiver in compliance with this section is not subject to criminal or civil liability or sanctions under Florida law.

(2) A physician shall not be subject to criminal or civil liability or sanctions under Florida law solely for issuing a physician certification with reasonable care to a person diagnosed with a debilitating medical condition in compliance with this section.

(3) Actions and conduct by a Medical Marijuana Treatment Center registered with the Department, or its agents or employees, and in compliance with this section and Department regulations, shall not be subject to criminal or civil liability or sanctions under Florida law.

(b) DEFINITIONS. For purposes of this section, the following words and terms shall have the following meanings:

(1) "Debilitating Medical Condition" means cancer, epilepsy, glaucoma, positive status for human immunodeficiency virus (HIV), acquired immune deficiency syndrome (AIDS), post-traumatic stress disorder (PTSD), amyotrophic lateral sclerosis (ALS), Crohn's disease, Parkinson's disease, multiple sclerosis, or other debilitating medical conditions of the same kind or class as or comparable to those enumerated, and for which a physician believes that the medical use of marijuana would likely outweigh the potential health risks for a patient.

(2) "Department" means the Department of Health or its successor agency.

(3) "Identification card" means a document issued by the Department that identifies a qualifying patient or a caregiver.

(4) "Marijuana" has the meaning given cannabis in Section 893.02(3), Florida Statutes (2014), and, in addition, "Low-THC cannabis" as defined in Section 381.986(1)(b), Florida Statutes (2014), shall also be included in the meaning of the term "marijuana."

(5) "Medical Marijuana Treatment Center" (MMTC) means an entity that acquires, cultivates, possesses, processes (including development of related products such as food, tinctures, aerosols, oils, or ointments),
transfers, transports, sells, distributes, dispenses, or administers marijuana, products containing marijuana, related supplies, or educational materials to qualifying patients or their caregivers and is registered by the Department.

(6) "Medical use" means the acquisition, possession, use, delivery, transfer, or administration of an amount of marijuana not in conflict with Department rules, or of related supplies by a qualifying patient or caregiver for use by the caregiver's designated qualifying patient for the treatment of a debilitating medical condition.

(7) "Caregiver" means a person who is at least twenty-one (21) years old who has agreed to assist with a qualifying patient's medical use of marijuana and has qualified for and obtained a

caregiver identification card issued by the Department. The Department may limit the number of qualifying patients a caregiver may assist at one time and the number of caregivers that a qualifying patient may have at one time. Caregivers are prohibited from consuming marijuana obtained for medical use by the qualifying patient.

(8) "Physician" means a person who is licensed to practice medicine in Florida.

(9) "Physician certification" means a written document signed by a physician, stating that in the physician's professional opinion, the patient suffers from a debilitating medical condition, that the medical use of marijuana would likely outweigh the potential health risks for the patient, and for how long the physician recommends the medical use of marijuana for the patient. A physician certification may only be provided after the physician has conducted a physical examination and a full assessment of the medical history of the patient. In order for a physician certification to be issued to a minor, a parent or legal guardian of the minor must consent in writing.

(10) "Qualifying patient" means a person who has been diagnosed to have a debilitating medical condition, who has a physician certification and a valid qualifying patient identification card. If the Department does not begin issuing identification cards within nine (9) months after the effective date of this section, then a valid physician certification will serve as a patient identification card in order to allow a person to become a "qualifying patient" until the Department begins issuing identification cards.

(c) LIMITATIONS.

(1) Nothing in this section allows for a violation of any law other than for conduct in compliance with the provisions of this section.

(2) Nothing in this section shall affect or repeal laws relating to nonmedical use, possession, production, or sale of marijuana.

(3) Nothing in this section authorizes the use of medical marijuana by anyone other than a qualifying patient.

(4) Nothing in this section shall permit the operation of any vehicle, aircraft, train or boat while under the influence of marijuana.

(5) Nothing in this section requires the violation of federal law or purports to give immunity under federal law.

(6) Nothing in this section shall require any accommodation of any on-site medical use of marijuana in any correctional institution or detention facility or place of education or employment, or of smoking medical marijuana in any public place.

(7) Nothing in this section shall require any health insurance provider or any government agency or authority to reimburse any person for expenses related to the medical use of marijuana.

(8) Nothing in this section shall affect or repeal laws relating to negligence or professional malpractice on the part of a qualified patient, caregiver, physician, MMTC, or its agents or employees.

(d) DUTIES OF THE DEPARTMENT. The Department shall issue reasonable regulations necessary for the implementation and enforcement of this section. The purpose of the regulations is to ensure the availability and safe use of medical marijuana by qualifying patients. It is the duty of the Department to promulgate regulations in a timely fashion.

(1) Implementing Regulations. In order to allow the Department sufficient time after passage of this section, the following regulations shall be promulgated no later than six (6) months after the effective date of this section:

a. Procedures for the issuance and annual renewal of qualifying patient identification cards to people with physician certifications and standards for renewal of such identification cards. Before issuing an identification card to a minor, the Department must receive written consent from the minor's parent or legal guardian, in addition to the physician certification.

b. Procedures establishing qualifications and standards for caregivers, including conducting appropriate background checks, and procedures for the issuance and annual renewal of caregiver identification cards.

c. Procedures for the registration of MMTCs that include procedures for the issuance, renewal, suspension and revocation of registration, and standards to ensure proper security, record keeping, testing, labeling, inspection, and safety.

d. A regulation that defines the amount of marijuana that could reasonably be presumed to be an adequate supply for qualifying patients' medical use, based on the best available evidence. This presumption as to quantity may be overcome with evidence of a particular qualifying patient's appropriate medical use.

(2) Identification cards and registrations. The Department shall begin issuing qualifying patient and caregiver identification cards, and registering MMTCs no later than nine (9) months after the effective date of this section.

(3) If the Department does not issue regulations, or if the Department does not begin issuing identification cards and registering MMTCs within the time limits set in this section, any Florida citizen shall have standing to seek judicial relief to compel compliance with the Department's constitutional duties.

(4) The Department shall protect the confidentiality of all qualifying patients. All records containing the identity of qualifying patients shall be confidential and kept from public disclosure other than for valid medical or law enforcement purposes.

(e) LEGISLATION. Nothing in this section shall limit the legislature from enacting laws consistent with this section.

(f) SEVERABILITY. The provisions of this section are severable and if any clause, sentence, paragraph or section of this measure, or an application thereof, is adjudged invalid by a court of competent jurisdiction other provisions shall continue to be in effect to the fullest extent possible.

Christian Bax

Christian Bax

Christian Bax is the Director of the Office of Compassionate Use for the Florida Department of Health. He is responsible for regulating the state's six dispensing organizations and overseeing the statewide Compassionate Use Registry. Mr. Bax has spent much of his career navigating heavily regulated business environments with previous experience in the fields of commercial agriculture, insurance, and cannabis licensure. Mr. Bax has a B.A. in Economics from the University of Alabama, a J.D. from the Florida State University College of Law, and a Masters of Business Administration from the The F.W. Olin Graduate School of Business at Babson College.

FLORIDA DEPARTMENT OF HEALTH

Office of Compassionate Use

Low-THC Cannabis & Medical Cannabis

CompassionateUse@flhealth.gov

Florida HEALTH

Rick Scott, Governor of the State of Florida
Celeste Philip. MD, MPH, State Surgeon General

Patients Under The Compassionate Medical Cannabis Act

- **Patient Requirements:**
  - Must be diagnosed with a qualifying condition
  - Must be a Florida resident
  - Must be a patient of the ordering physician for the immediately preceding 3 months

- **Low-THC Cannabis Conditions:**
  - Cancer
  - Epilepsy
  - Chronic seizures
  - Chronic muscle spasms

- **Medical Cannabis Conditions:**
  - Terminal Conditions

  Two physicians must certify that a patient's condition will be fatal within one year, if it runs its normal course.

Dispensing Organizations

Dispensing Organization Requirements:

- Possess a valid certificate of registration issued by DACS for the cultivation of more than 400,000 plants.
- Operate as a registered nursery in Florida for 30 continuous year.
- All owners and managers must clear a Level 2 background screening pursuant to section 435.04, F.S.
- Five initial licenses were awarded pursuant to SB 1030, two more have been subsequently awarded pursuant to 381.986, F.S.
- Current law provides for three additional licenses once 250,000 patients are enrolled in the compassionate use registry.

Authorization Timeline

Following the approval by the Department, each dispensing organization must:

- Submit a $5 million performance bond within 10 business days of receiving approval.
- Successfully complete an inspection for cultivation authorization within 75 days of receiving approval.
- After successfully completing inspections for processing and dispensing authorization, begin dispensing to patients within 210 days of initial approval.

7 Approved Dispensing Organizations

Dispensing Organization	Authorization Stage	Locations
Trulieve	Dispensing	Tallahassee, Clearwater, Tampa, delivery
Surterra Therapeutics	Dispensing	Tampa, delivery
Modern Health Concepts	Dispensing	Miami, delivery
Knox Medical	Dispensing	Delivery
CHT Medical	Dispensing	Delivery
The Green Solution	Cultivating	*N/A*
Grow Healthy	*N/A*	*N/A*

Ordering Breakdown

- **Registered Patients: 1,800**
- **Low-THC Cannabis Dispensed (mg): 6,000,000**
- **Medical Cannabis Dispensed (mg): 3,000,000**
- **Method of Dispensation:**
  - Storefront: 51%
  - Delivery: 49%

How The OCU Registry Works

- **Step 1:** A physician diagnoses a patient with a qualifying condition.
- **Step 2:** The physician treats the patient for 3 months, and obtains written informed consent.
- **Step 3:** The physician submits a treatment plan to the University of Florida College of Pharmacy each quarter or if the plan changes.
- **Step 4:** The physician enters the order into the Compassionate Use Registry. Physicians must designate a route of administration, the recommended amount per dose, and the number of doses per day.
- **Step 5:** The patient may fill the order with any one of the six approved dispensing organizations.

Lessons From Other States

Preventing Diversion:

- Seed-to-Sale Tracking (Ex. Colorado, Hawaii, Nevada, Washington, New York, New Mexico, Illinois, etc.)
- Personal Possession Limits (Ex. Colorado, Washington, Illinois, Nevada)

Public Health and Safety:

- Packaging, Labeling, and Marketing Requirements (Ex. Colorado, Connecticut, Massachusetts)
- Policing Intoxicated Driving (Ex. Colorado, Nevada, Pennsylvania)
- Leveraging Agency Experience (Etc. Colorado, Washington, Oregon)

Bertha Madras, PhD

Bertha K. Madras, PhD

Bertha K. Madras, PhD, is a professor of psychobiology in the Department of Psychiatry at Harvard Medical School. She is former Deputy Director for Demand Reduction (prevention, treatment) in the White House Office of National Drug Control Policy, Executive Office of President, a position unanimously confirmed by the US Senate.

Her research focuses on the relevance of dopamine signaling to addiction biology, ADHD, and Parkinson's disease. She holds 19 patents for novel brain imaging agents and candidate therapeutics. In public service, she has delivered over 250 public presentations globally, and developed a museum exhibit and a CD (licensed by Disney), with the Museum of Science, Boston. A recipient of an NIH MERIT award, NIDA Public Service Award, American Academy of Addiction Psychiatry Founders' Award, and others, her brain imaging agent altropane, was listed by The Better World Report as "one of 25 technology transfer innovations that changed the world".

Marijuana as Medicine

Disclosure

I disclose the following relationships (financial and non-financial) with entities over past year that may be relevant to the content I am presenting:

Rivermend Health, Scientific Advisory Board
National Football League, Advisory Board (-2015)
World Health Organization
U.S. Department of Justice
Vatican Pontifical Academy of Sciences

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Marijuana for medicinal: 25 States; Washington, DC
Cannabidiol (CBD) preparations: 16 States

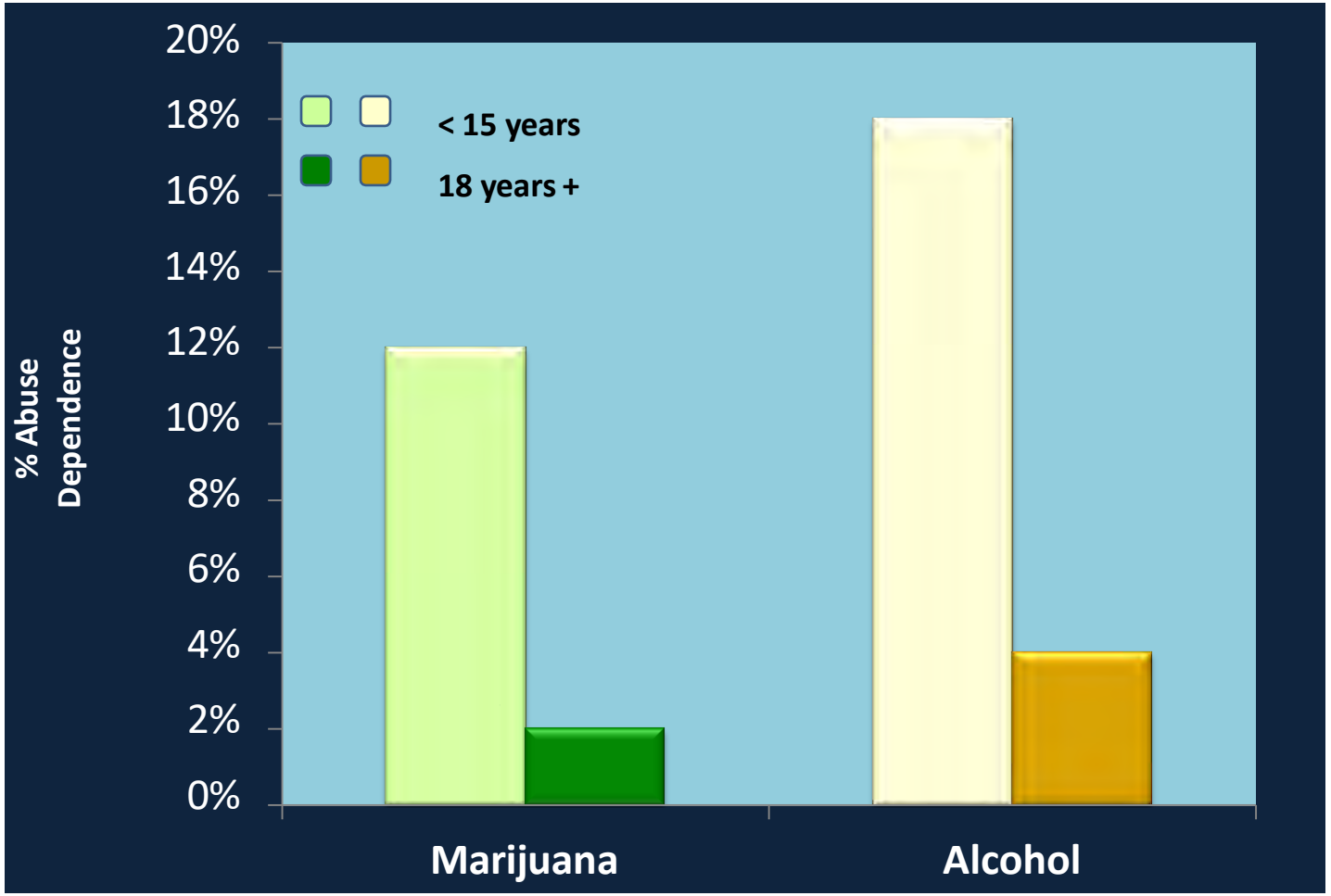
Drivers of the Movement

- Fulfill unmet needs (pain, medical, psychiatric problems)
- Grass roots activism
- To normalize use for multiple purposes
- Profits, political influence, marketing ingenuity

Is evidence scientifically based?

- Scientific evidence: disputed or disregarded
- Gaps in knowledge: ignored
- Unintended consequences: ignored or unknown

Addiction to Marijuana, Alcohol Higher Among Young Adolescent Initiators

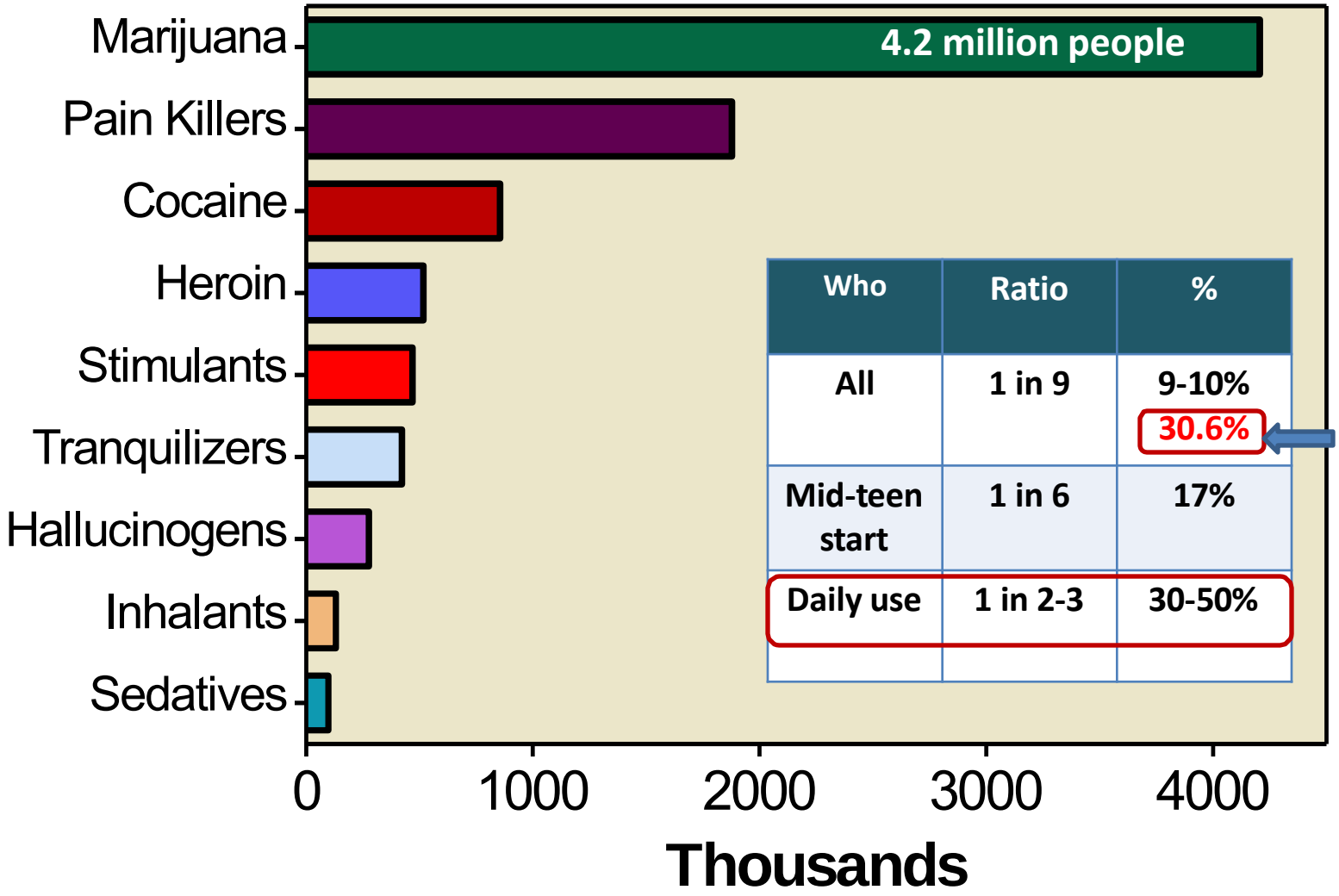


Source: SAMHSA, *2013 National Survey on Drug Use and Health* (September 2014)

Cannabis Use Disorder Prevalence

Greater Use; Greater Numbers with Cannabis Use Disorder

Adolescents at higher risk



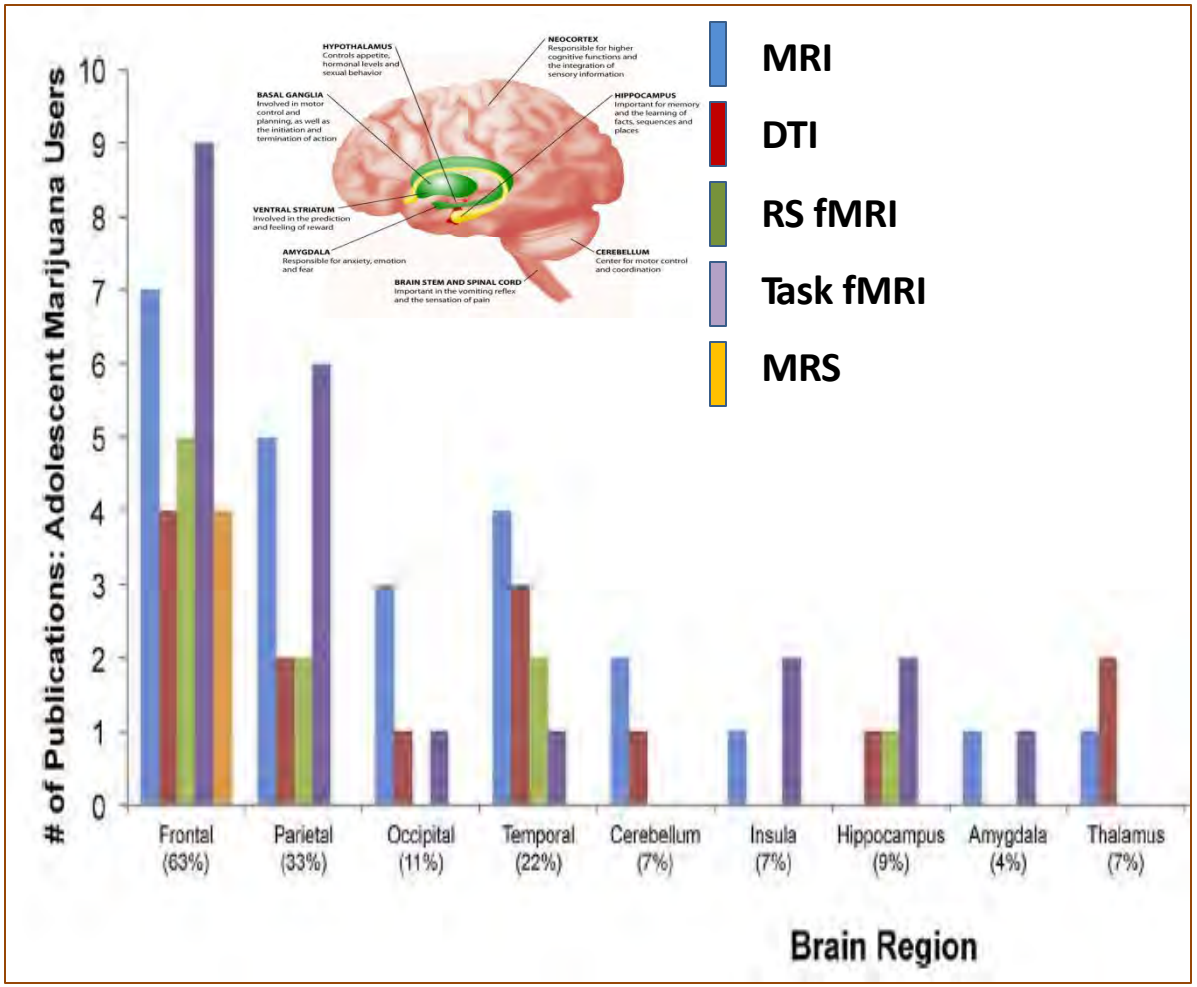
Who	Ratio	%
All	1 in 9	9-10% 30.6%
Mid-teen start	1 in 6	17%
Daily use	1 in 2-3	30-50%

Most recent data

Center for Behavioral Health Statistics and Quality. (2015). *Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUH* Series H-50). Retrieved from http://www.samhsa.gov/data/

Hasin DS, Saha TD, Kerridge BT, Goldstein RB, Chou SP, Zhang H, Jung J, Pickering RP, Ruan WJ, Smith SM, Huang B, Grant BF. Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013. JAMA Psychiatry. 2015 Dec 1;72(12):1235-42.

Significant Brain Changes in Adolescent Marijuana Users: 46 MRI studies



Conclusions:

- **Marijuana-related brain changes**
- **Robust in adolescent brain**
- **Some associated with impaired function**

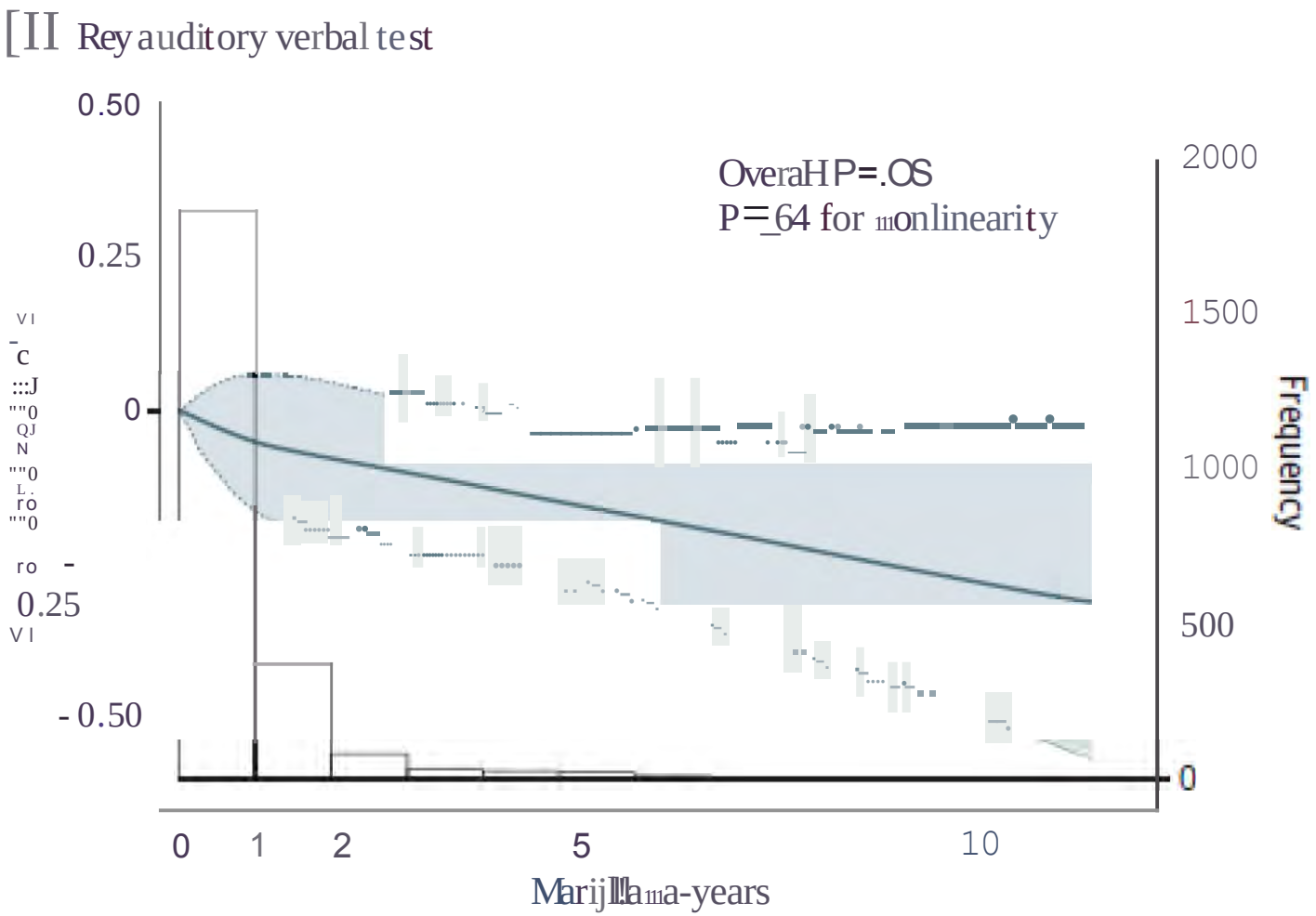
Silveri, M.M., et al., Neurobiological signatures associated with alcohol and drug use in the human adolescent brain. Neurosci. Biobehav. Rev. (2016), http://dx.doi.org/10.1016/j.neubiorev.2016.06.042

Early, Persistent Marijuana Use Associated with Reduced I.Q.

IQ drop associated: with length of time addicted
IQ drop most: if use before age 18, addicted at 38
IQ reduced: if did not quit use at age 38
IQ still reduced: if use before 18 and then quit

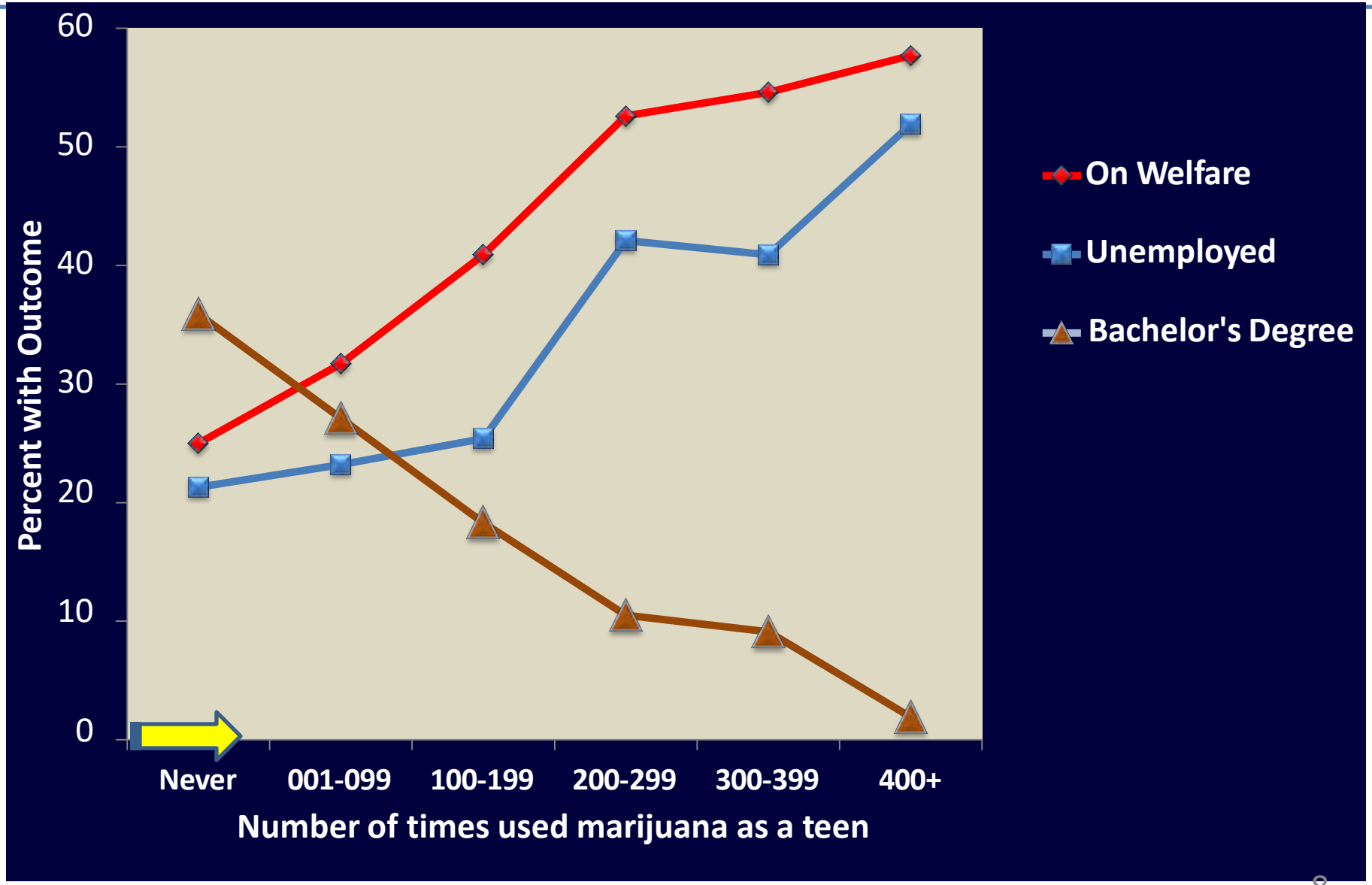
Meier et al, Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc. Natl. Acad. Sci *USA,* 2012 Oct 2;109(40):E2657-64.

Memory Impairment: Long Term Marijuana Use



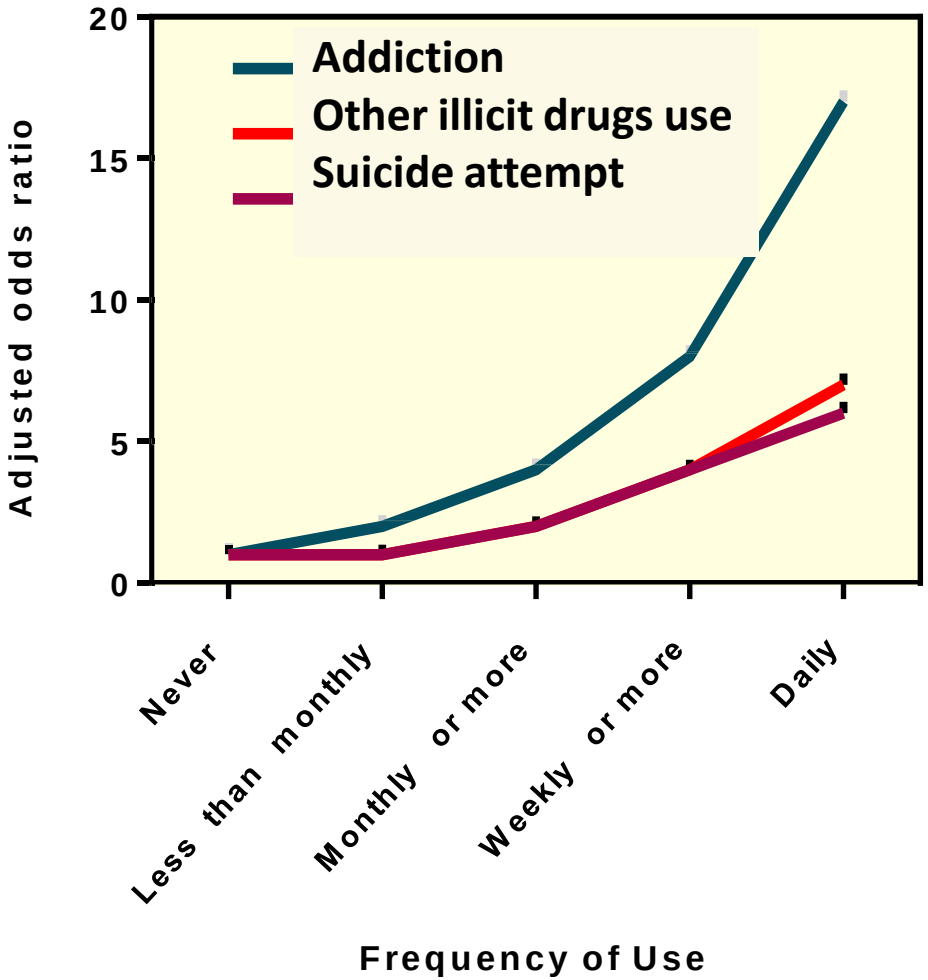
Reto Auer, Eric Vittinghoff, Kristine Yaffe, Arnaud Kunzi, Stefan G. Kertesz, Deborah A. Levine, Emiliano Albanese, Rachel A. Whitmer, David R. Jacobs Jr, Stephen Sidney, M. Maria Glymour, Mark J. Pletcher Association Between Lifetime Marijuana Use and Cognitive Function in Middle Age The Coronary Artery Risk Development in Young Adults (CARDIA) Study, *JAMA Intern Med. 2016;176(3):352-361. doi:10.1001/jamainternmed.2015.7841*

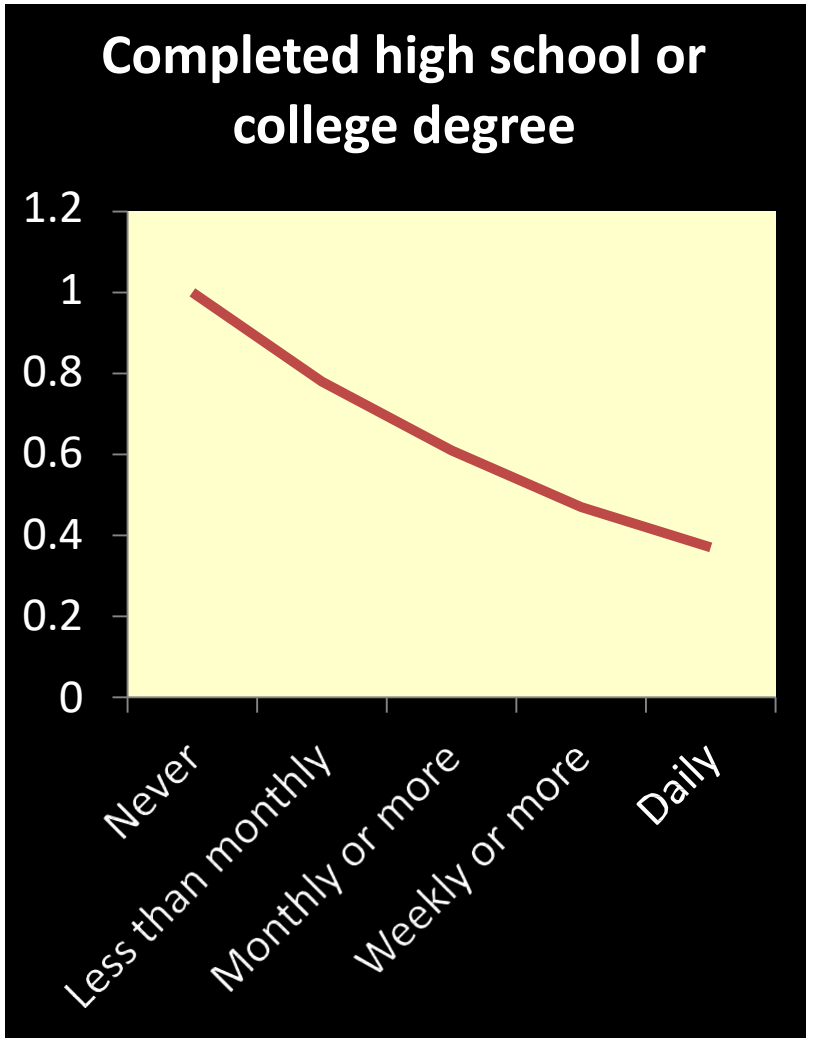
Teen Marijuana Use Affects Adult Motivation



Source: Fergusson and Boden , Addiction, 103, pp. 969-976, 2008.

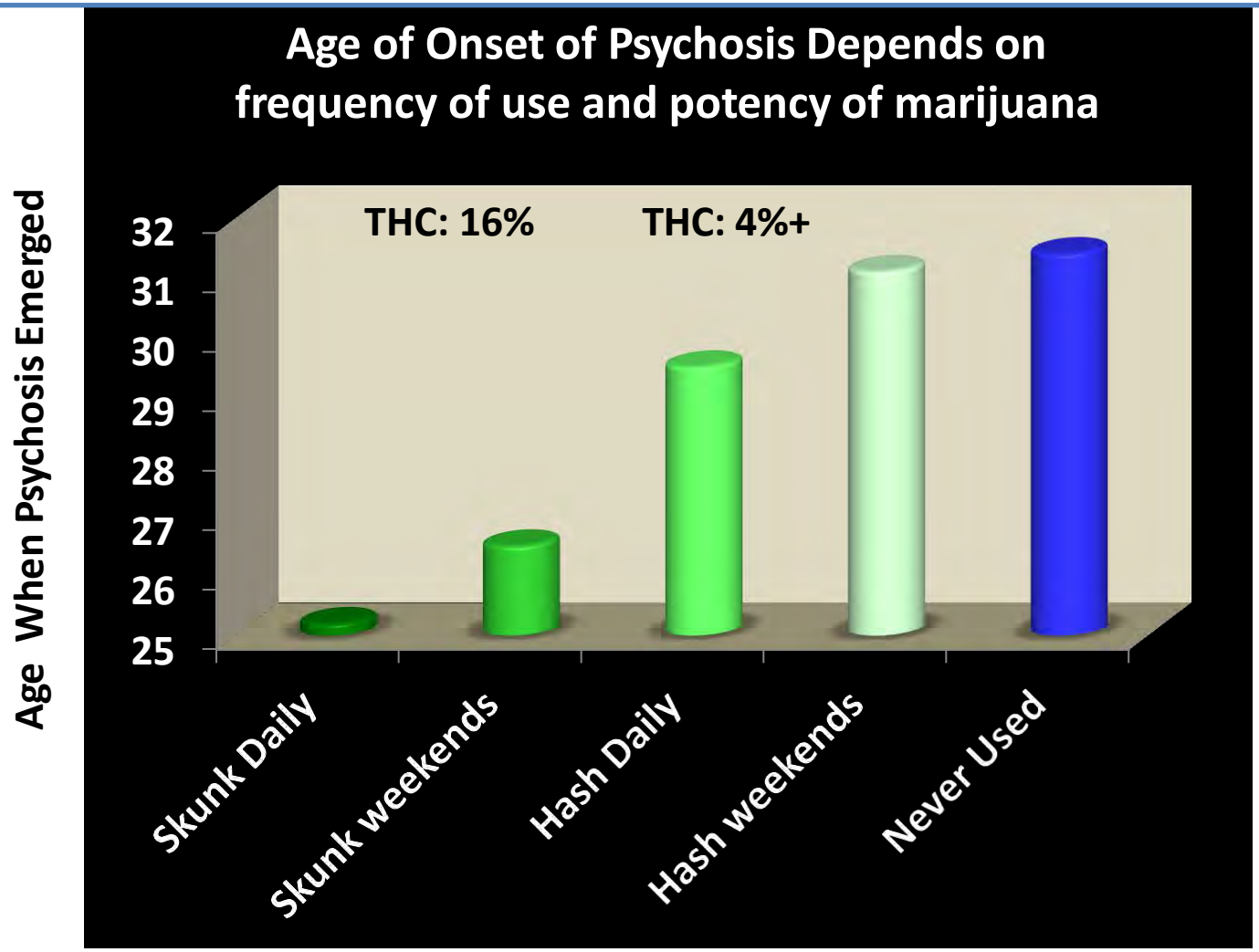
The More Marijuana Use, the Worse the Outcomes





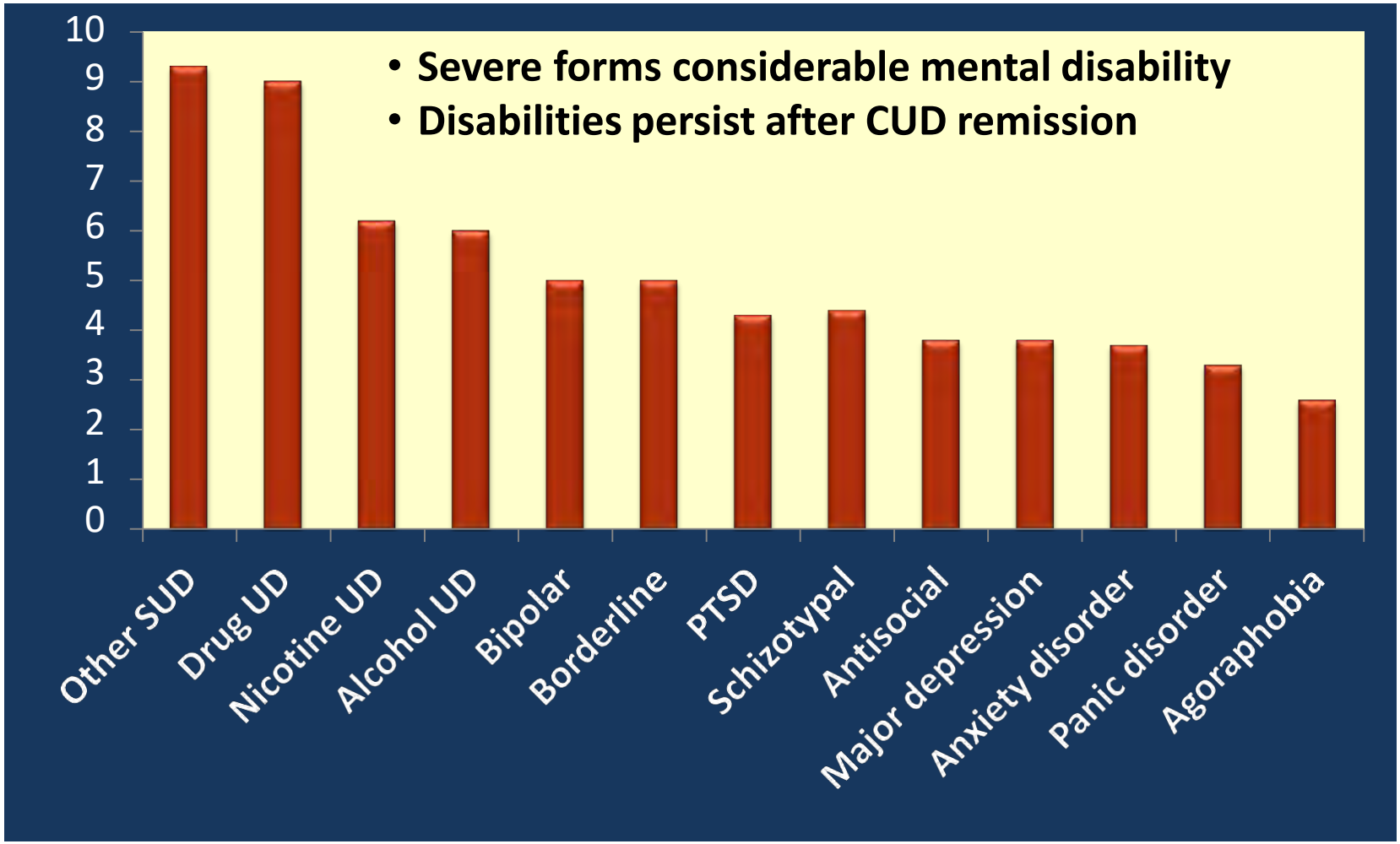
Silins et al, Lancet Psychiatry 1: 286–93, 2014; n= 2537-3765; 13-30 years

Strength and Frequency of Marijuana Use Lowers Age When Psychosis Appears



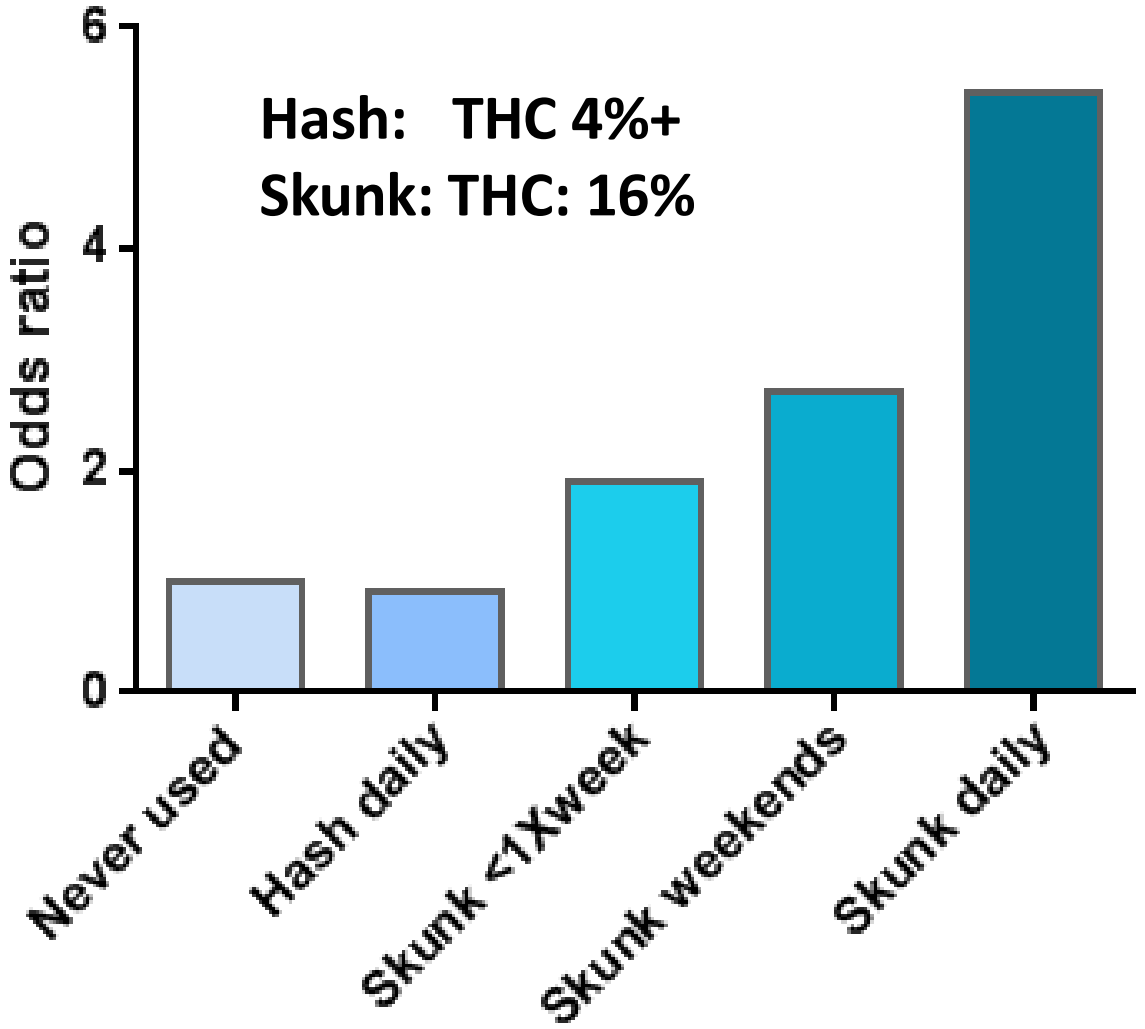
Di Forti et al. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. Schizophr Bull. 2014 Nov;40(6):1509-17

Marijuana Use Disorder Associated with Other Significant Mental Disorders



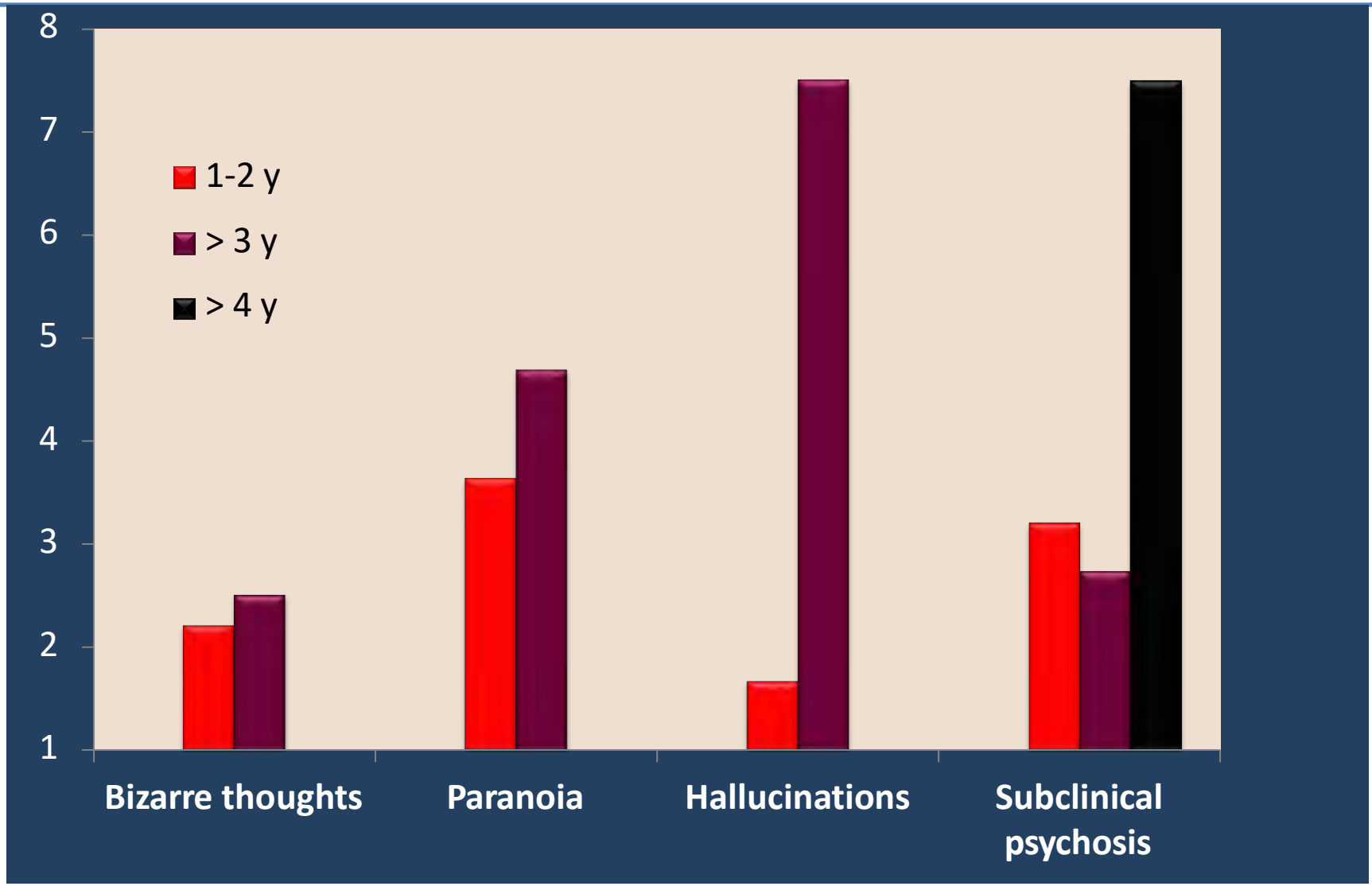
Hasin DS, Kerridge BT, Saha TD, Huang B, Pickering R, Smith SM, Jung J, Zhang H, Grant BF. Prevalence and Correlates of DSM-5 marijuana Use Disorder, 2012-2013: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions-III. Am J Psychiatry. 2016 Mar 4:appiajp201515070907. [Epub ahead of print]

Psychosis: Strength and Frequency of Marijuana Use Increases Risk of Psychosis



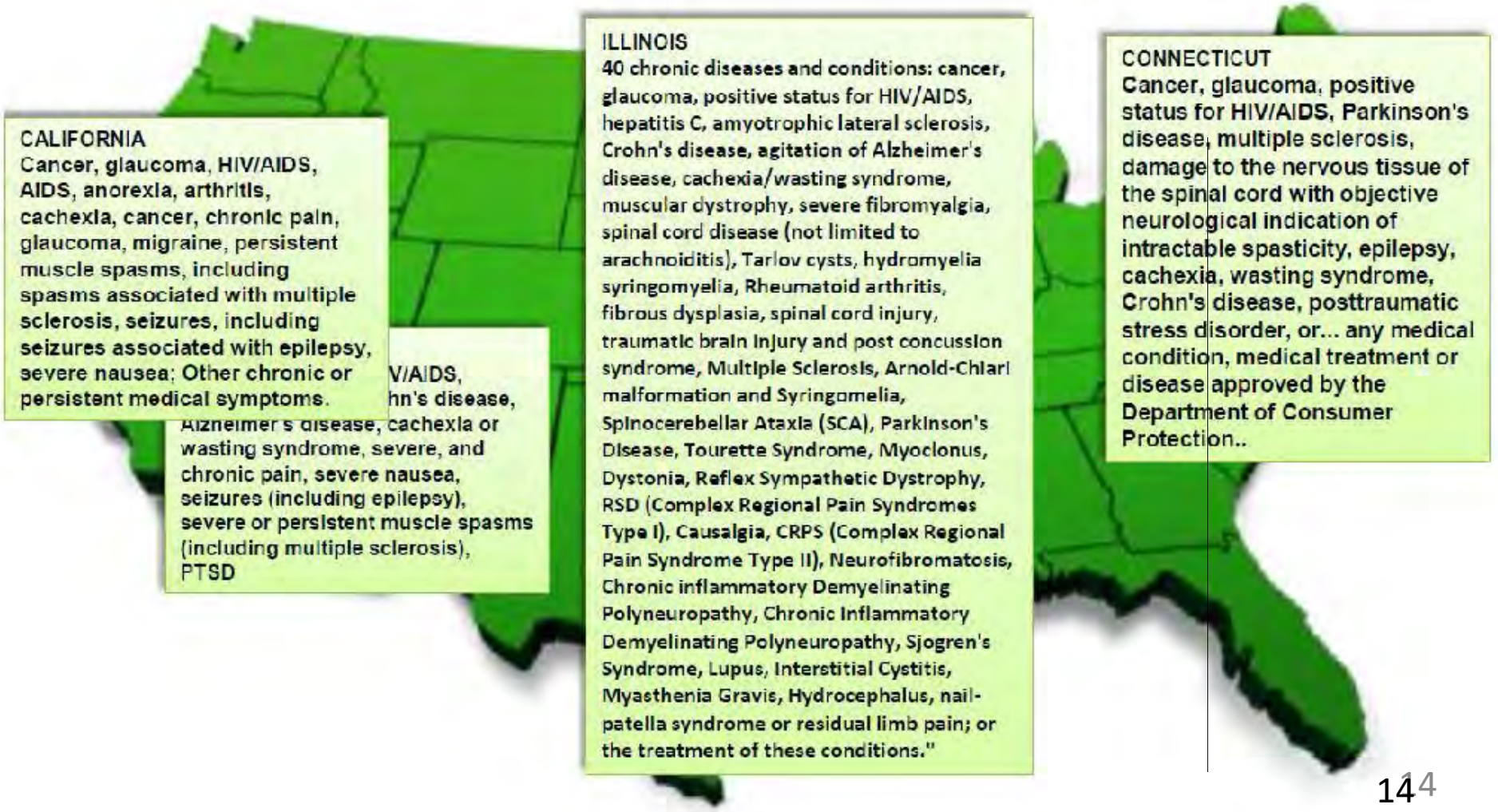
Di Forti et al Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. The Lancet Psychiatry 2:233-238, 2015

Psychosis: Adolescent Weekly Marijuana Users



Bechtold et al, Am J Psychiatry 173:8, August 2016

State Regulations for Medical Conditions
No Rational Basis



CALIFORNIA
Cancer, glaucoma, HIV/AIDS, AIDS, anorexia, arthritis, cachexia, cancer, chronic pain, glaucoma, migraine, persistent muscle spasms, including spasms associated with multiple sclerosis, seizures, including seizures associated with epilepsy, severe nausea; Other chronic or persistent medical symptoms.

V/AIDS,
hn's disease,
Alzheimer's disease, cachexia or wasting syndrome, severe, and chronic pain, severe nausea, seizures (including epilepsy), severe or persistent muscle spasms (including multiple sclerosis), PTSD

ILLINOIS
40 chronic diseases and conditions: cancer, glaucoma, positive status for HIV/AIDS, hepatitis C, amyotrophic lateral sclerosis, Crohn's disease, agitation of Alzheimer's disease, cachexia/wasting syndrome, muscular dystrophy, severe fibromyalgia, spinal cord disease (not limited to arachnoiditis), Tarlov cysts, hydromyelia syringomyelia, Rheumatoid arthritis, fibrous dysplasia, spinal cord injury, traumatic brain injury and post concussion syndrome, Multiple Sclerosis, Arnold-Chiari malformation and Syringomelia, Spinocerebellar Ataxia (SCA), Parkinson's Disease, Tourette Syndrome, Myoclonus, Dystonia, Reflex Sympathetic Dystrophy, RSD (Complex Regional Pain Syndromes Type I), Causalgia, CRPS (Complex Regional Pain Syndrome Type II), Neurofibromatosis, Chronic inflammatory Demyelinating Polyneuropathy, Chronic Inflammatory Demyelinating Polyneuropathy, Sjogren's Syndrome, Lupus, Interstitial Cystitis, Myasthenia Gravis, Hydrocephalus, nail-patella syndrome or residual limb pain; or the treatment of these conditions."

CONNECTICUT
Cancer, glaucoma, positive status for HIV/AIDS, Parkinson's disease, multiple sclerosis, damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity, epilepsy, cachexia, wasting syndrome, Crohn's disease, posttraumatic stress disorder, or... any medical condition, medical treatment or disease approved by the Department of Consumer Protection..

Meta-analyses:

Evidence For Whole Plant Marijuana Poor Quality, Or Does Not Exist

- Andrade C. Cannabis and Neuropsychiatry, 2: The Longitudinal Risk of Psychosis as an Adverse Outcome. J Clin Psychiatry. 2016 Jun;77(6):e739-42.
- Andreae MH, et al., Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. J Pain. 2015 Dec;16(12):1221-32
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- Gibbs M, et al,Cannabis use and mania symptoms: a systematic review and meta-analysis. J Affect Disord. 2015 Jan 15;171:39-47
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- Lutge EE, et al, The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. Cochrane Database Syst Rev. 2013
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- Phillips TJ, et al. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. PLoS One. 2010 Dec 28;5(12):e14433.
- Richards BL, et al Neuromodulators for pain management in rheumatoid arthritis. Cochrane Database Syst Rev. 2012 Jan 18;1:CD008921
- van den Elsen GA, et al., Efficacy and safety of medical cannabinoids in older subjects: a systematic review. Ageing Res Rev. 2014 Mar;14:56-64.
- Whiting PF et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73
- Wilkinson ST, et al, A Systematic Review of the Evidence for Medical Marijuana in Psychiatric Indications. J Clin Psychiatry. 2016 Aug;77(8):1050-64.
- Yadav V, , et al., Summary of evidence-based guideline: complementary and alternative medicine in multiple sclerosis: report of the guideline development subcommittee of the American Academy of Neurology. Neurology. 2014 Mar 25;82(12):1083- 92.

Dementia

Neurological diseases

Multiple sclerosis

Psychiatric disorders

Epilepsy

Cancer therapy

Chronic pain

Arthritis

Chronic neuropathic pain

Medical, psychiatric illnesses

Movement disorders

AIDS

Bowel diseases

Why is Whole Plant Marijuana Not A Good Candidate?

Unpurified plant with at least 750 chemicals of unknown actions and interactions

Inconsistent doses of THC, CBD and other components

Smoking is most frequent route, a potential hazard to lung health and rapid brain entry;

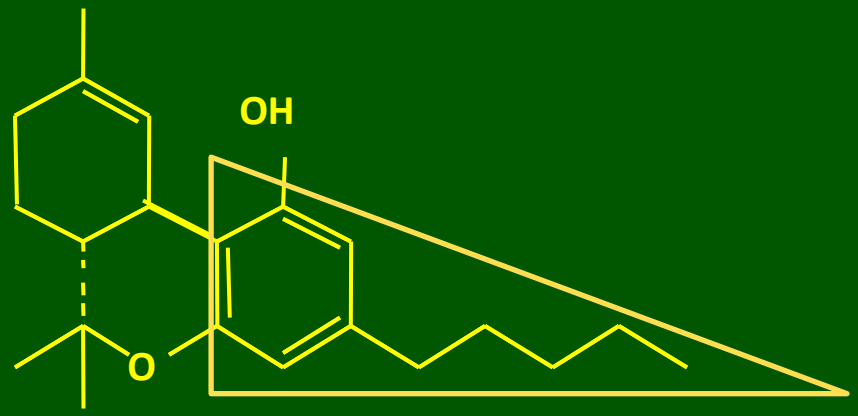
Data on edibles, vaporized zero or limited

Cognitive- and motor-impairing limit its usefulness

Marijuana Chemistry

marijuana sativa contains ~ 750 chemicals

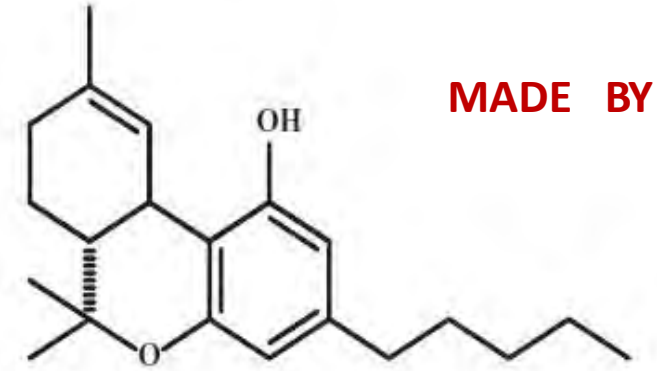
D ^{9}-TetraHydroCannabinol (THC) highest



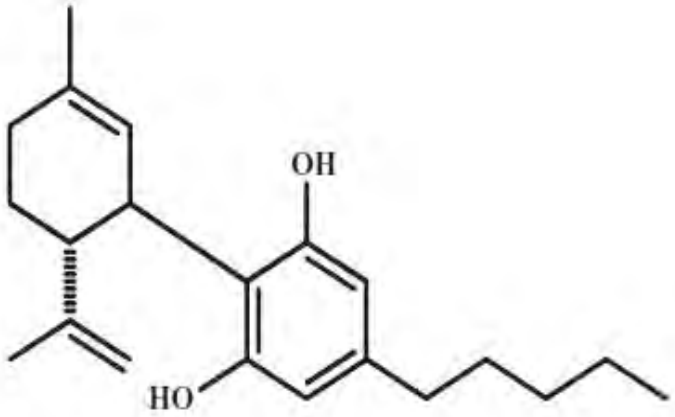
- ~104 *Phyto*cannabinoids, 200-300 terpenoids
- *Synthetic* cannabinoids: 1,000's made by chemists
- *Endo*cannabinoids: Made by brain, body

Cannabinoids in Plant Differ from Endocannabinoids in Brain

MADE BY PLANT

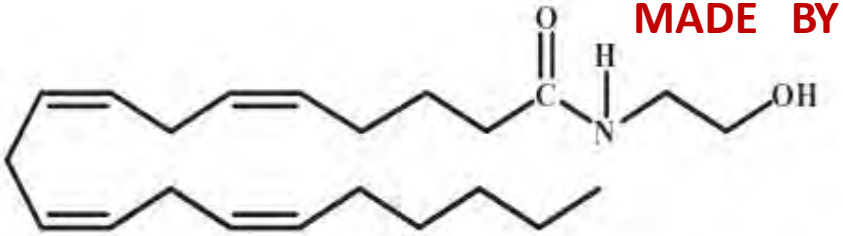


Δ^9-tetrahydrocannabinol (Δ^9-THC)

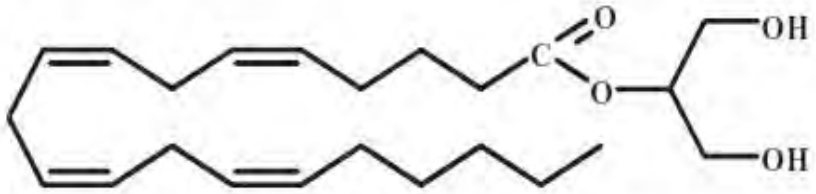


cannabidiol (CBD)

MADE BY BRAIN

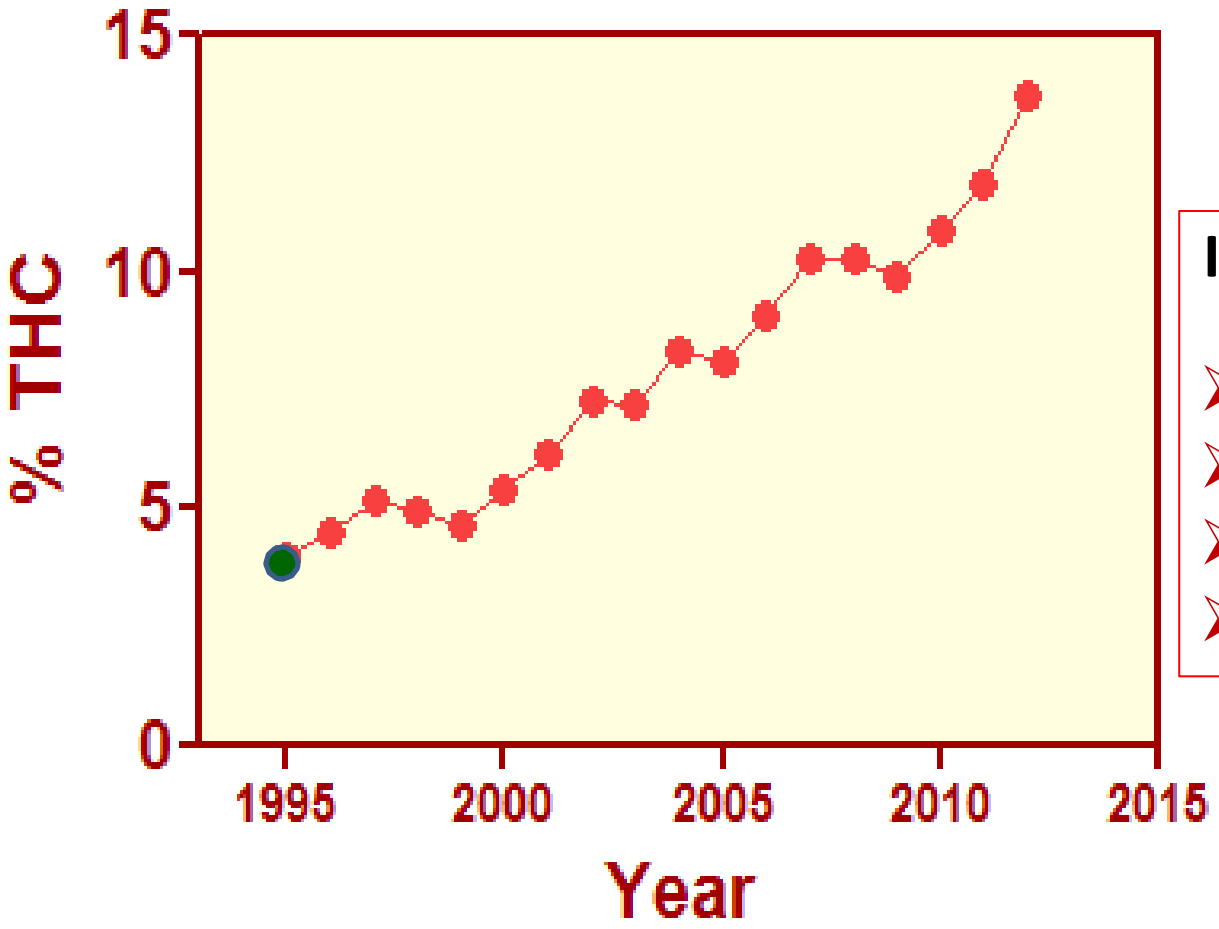


arachidonoyl ethanolamide (anandamide)



2-arachidonoyl glycerol (2-AG)

Potency Risk: Marijuana Potency (THC) Rising Rapidly



Implications for:

- **Driving**
- **Addiction**
- **Toxicity**
- **Psychosis**

Source: MA ElSohly, NIDA Marijuana Project, **POTENCY MONITORING PROGRAM QUARTERLY REPORT NUMBER 119** REPORTING PERIOD: *09/16/2012 - 12/15/2012*

Marijuana smoke: >700 Chemicals; like Tobacco Smoke

❖ But marijuana has

20X more ammonia levels

5X more hydrogen cyanide

more tar, benzene, toluene, cancer- causing hydrocarbons

Chemical	TOBACCO	MARIJUANA
naphthalene	4908	4459
1-methylnaphthalene	4888	4409
2-methylnaphthalene	3666	2917*
		459*
		213*
		659*
		476
		136*
		117*
		82.8*
		43.1*
		56.3
		16.2*
		1.54*
		12.6*
		15.5*
		6.10*
		8.65
		2.83*
dibenz(a,l)pyrene	<0.634	
dibenz(a,e)pyrene	<0.313	
dibenz(a,i)pyrene	2.55	
dibenz(a,h)pyrene	<0.354	

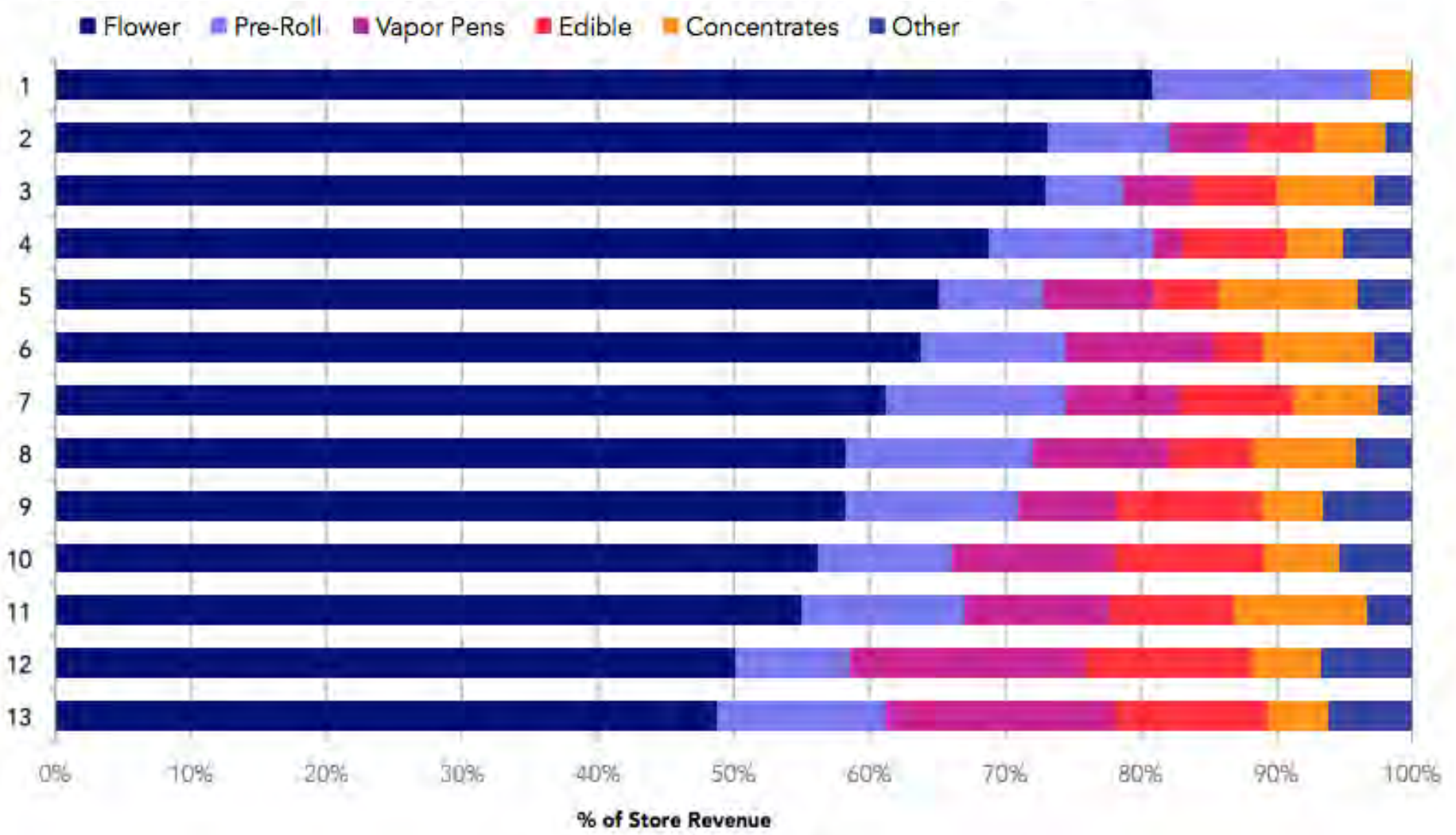
Extreme		
Chemical	TOBACCO	MARIJUANA
NAT	125	<1.87*
Selenium	4.42–14.7	4.42–14.7

Moir et al, A Comparison of Mainstream and Sidestream Marijuana and Tobacco Cigarette Smoke Produced under Two Machine Smoking Conditions. *Chem. Res. Toxicol.*, 2008, *21* (2), 494–502

Ratio of THC:CBD climbing

EFFECT	THC	CBD
Reward	Yes	No (anti?)
Intoxication	Yes	No (anti?)
Impairs cognition	Yes	No (anti?)
Anxiety	Yes	Anxiolytic (?)
Psychotomimetic	Yes	Anti-psychotic (?)
Seizures	Yes	Anti-convulsant (?)
Receptors	CB1, CB2, others	FAAH (?), TRPV-1,2(?), 5-HT1A
Addiction	Yes	No? Treatment?

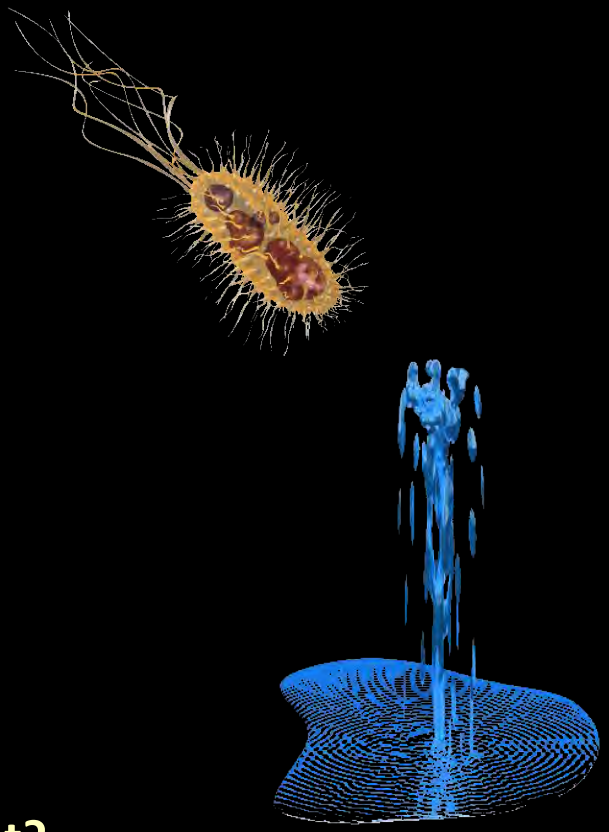
Different Dispensaries Sell Different Products



Chemistry, Quality Control?

Variables

- Soil
- Water
- Temperature
- Bacteria
- Viruses
- Animal Waste
- Insecticides
- Pesticides
- Herbicides
- Insects
- Toxic Chemicals
- Active Compounds
- Heavy Metals
- Drug Content of plant?



The Future
Doctor-patient Relationship

- **Bona fide relationship:** Include medical exam, medical record, long term follow-up care.
- **Diagnosis:** Should be legitimate and not a diffuse complaint
- **Screening for at risk patients:** All patients should be screened for psychiatric problems, problematic substance use or substance use disorder
- **Long term recommendation:** No patient should have recommendation that exceeds initially short term use; and no longer than one year
- **Reporting requirements:** All adverse events associated with marijuana use, addiction, accidents, employment difficulties, should be reportable to state authorities.

The Future

For Purveyors of Marijuana, CBD Preparations

- **Dose**: All preparations should have printed and documented doses of THC, CBD and cannabinol content, and claim that they are herbicide, pesticide, insecticide, and pyrogen-free, at minimum, with known shelf live.
- **Dose:** Any dose above 12% THC needs justification
- **Dose:** For a given dose and route (e.g. edibles), pharmacokinetic properties should be known
- **Packet inserts:** include disclaimers (no FDA approval, no production complies with FDA requirements for manufacturing or claims.
- **Packet inserts:** Risks (e.g. impairment, addiction,driving)
- **Packet inserts**: Drug-drug interactions
- **Packet inserts:** Pharmacokinetic properties of each type of preparation
- **Medical claims:** All medical claims of marijuana preparations and dose should be sustained and require citations of high quality clinical trials
- **Dispensary personnel:** need training in accuracy of recommendations
- **Recommendations:** need tempering with absence of evidence

Resources: World Health, NIDA

- **December, 2015:** World Health Organization, Expert Committee on Drug Dependence, a branch of the Essential Medicines issued:
- BK Madras; Update on Cannabis and its Medical Use http://www.who.int/medicines/access/controlled-substances/6_2_cannabis_update.pdf.

- **April 2016:** the World Health Organization issued a report *The Health and Social Effects of Nonmedical Cannabis Use, multiple authors*
- http://www.who.int/substance_abuse/publications/cannabis_report/en/

- **March 2016:** Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, Gonzalez R, Bloomfield MA, Curran HV, Baler R. Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review. JAMA Psychiatry. 2016 73(3):292-7.

- **June 2014:** Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014;370(23):2219-27.

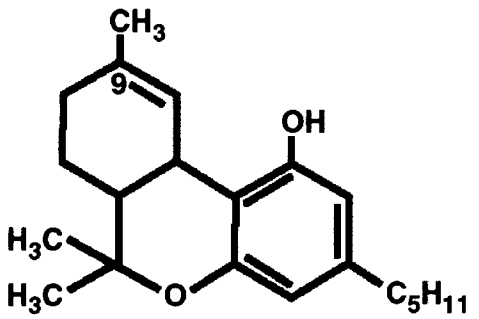
500012 Rev Sep 2004

MARINOL® CIII

(Dronabinol)
Capsules
R_x only

DESCRIPTION

Dronabinol is a cannabinoid designated chemically as (*6aR-trans*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol. Dronabinol has the following empirical and structural formulas:



$C_{21}H_{30}O_2$ (molecular weight = 314.47)

Dronabinol, the active ingredient in MARINOL® Capsules, is synthetic delta-9-tetrahydrocannabinol (delta-9-THC). Delta-9-tetrahydrocannabinol is also a naturally occurring component of *Cannabis sativa L.* (Marijuana).

Dronabinol is a light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Dronabinol is insoluble in water and is formulated in sesame oil. It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7.

Capsules for oral administration: MARINOL® Capsules is supplied as round, soft gelatin capsules containing either 2.5 mg, 5 mg, or 10 mg dronabinol. Each MARINOL® Capsule is formulated with the following inactive ingredients: FD&C Blue No. 1 (5 mg), FD&C Red No. 40 (5 mg), FD&C Yellow No. 6 (5 mg and 10 mg), gelatin, glycerin, methylparaben, propylparaben, sesame oil, and titanium dioxide.

CLINICAL PHARMACOLOGY

Dronabinol is an orally active cannabinoid which, like other cannabinoids, has complex effects on the central nervous system (CNS), including central sympathomimetic activity. Cannabinoid receptors have been discovered in neural tissues. These receptors may play a role in mediating the effects of dronabinol and other cannabinoids.

Pharmacodynamics

Dronabinol-induced sympathomimetic activity may result in tachycardia and/or conjunctival injection. Its effects on blood pressure are inconsistent, but occasional subjects have experienced orthostatic hypotension and/or syncope upon abrupt standing.

Dronabinol also demonstrates reversible effects on appetite, mood, cognition, memory, and perception. These phenomena appear to be dose-related, increasing in frequency with higher dosages, and subject to great interpatient variability.

After oral administration, dronabinol has an onset of action of approximately 0.5 to 1 hours and peak effect at 2 to 4 hours. Duration of action for psychoactive effects is 4 to 6 hours, but the appetite stimulant effect of dronabinol may continue for 24 hours or longer after administration.

Tachyphylaxis and tolerance develop to some of the pharmacologic effects of dronabinol and other cannabinoids with chronic use, suggesting an indirect effect on sympathetic neurons. In a study of the pharmacodynamics of chronic dronabinol exposure, healthy male volunteers (N = 12) received 210 mg/day dronabinol, administered orally in divided doses, for 16 days. An initial tachycardia induced by dronabinol was replaced successively by normal sinus rhythm and then bradycardia. A decrease in supine blood pressure, made worse by standing, was also observed initially. These volunteers developed tolerance to the cardiovascular and subjective adverse CNS effects of dronabinol within 12 days of treatment initiation.

Tachyphylaxis and tolerance do not, however, appear to develop to the appetite stimulant effect of MARINOL® Capsules. In studies involving patients with Acquired Immune Deficiency Syndrome (AIDS), the appetite stimulant effect of MARINOL® Capsules has been sustained for up to five months in clinical trials, at dosages ranging from 2.5 mg/day to 20 mg/day.

Pharmacokinetics

Absorption and Distribution: MARINOL® (Dronabinol) Capsules is almost completely absorbed (90 to 95%) after single oral doses. Due to the combined effects of first pass hepatic metabolism and high lipid solubility, only 10 to 20% of the administered dose reaches the systemic circulation. Dronabinol has a large apparent volume of distribution, approximately 10 L/kg, because of its lipid solubility. The plasma protein binding of dronabinol and its metabolites is approximately 97%.

The elimination phase of dronabinol can be described using a two compartment model with an initial (alpha) half-life of about 4 hours and a terminal (beta) half-life of 25 to 36 hours. Because of its large volume of distribution, dronabinol and its metabolites may be excreted at low levels for prolonged periods of time.

The pharmacokinetics of dronabinol after single doses (2.5, 5, and 10 mg) and multiple doses (2.5, 5, and 10 mg given twice a day; BID) have been studied in healthy women and men.

Summary of Multiple-Dose Pharmacokinetic Parameters of Dronabinol in Healthy Volunteers (n=34; 20-45 years) under Fasted Conditions

Mean (SD) PK Parameter Values			
BID Dose	**Cmax ng/mL**	**Median Tmax (range), hr**	**AUC(0-12) ng•hr/mL**
2.5 mg	1.32 (0.62)	1.00 (0.50-4.00)	2.88 (1.57)
5 mg	2.96 (1.81)	2.50 (0.50-4.00)	6.16 (1.85)
10 mg	7.88 (4.54)	1.50 (0.50-3.50)	15.2 (5.52)

A slight increase in dose proportionality on mean Cmax and AUC (0-12) of dronabinol was observed with increasing dose over the dose range studied.

Metabolism: Dronabinol undergoes extensive first-pass hepatic metabolism, primarily by microsomal hydroxylation, yielding both active and inactive metabolites. Dronabinol and its principal active metabolite, 11-OH-delta-9-THC, are present in approximately equal concentrations in plasma. Concentrations of both parent drug and metabolite peak at approximately 0.5 to 4 hours after oral dosing and decline over several days. Values for clearance average about 0.2 L/kg-hr, but are highly variable due to the complexity of cannabinoid distribution.

Elimination: Dronabinol and its biotransformation products are excreted in both feces and urine. Biliary excretion is the major route of elimination with about half of a radio-labeled oral dose being recovered from the feces within 72 hours as contrasted with 10 to 15% recovered from urine. Less than 5% of an oral dose is recovered unchanged in the feces.

Following single dose administration, low levels of dronabinol metabolites have been detected for more than 5 weeks in the urine and feces.

In a study of MARINOL® Capsules involving AIDS patients, urinary cannabinoid/creatinine concentration ratios were studied bi-weekly over a six week period. The urinary cannabinoid/creatinine ratio was closely correlated with dose. No increase in the cannabinoid/creatinine ratio was observed after the first two weeks of treatment, indicating that steady-state cannabinoid levels had been reached. This conclusion is consistent with predictions based on the observed terminal half-life of dronabinol.

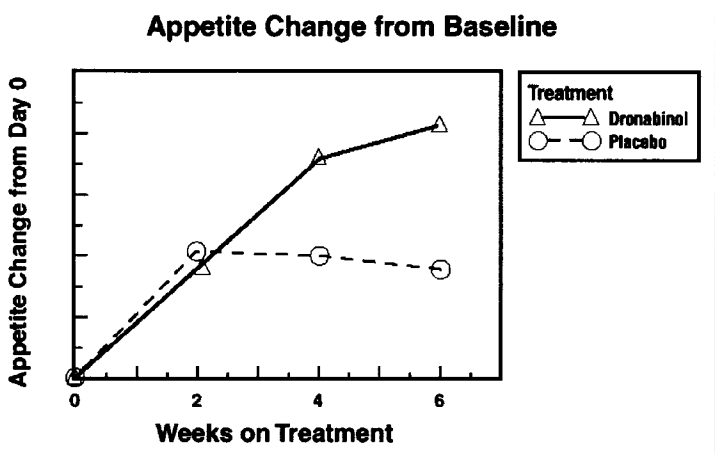
Special Populations: The pharmacokinetic profile of MARINOL® Capsules has not been investigated in either pediatric or geriatric patients.

Clinical Trials

Appetite Stimulation: The appetite stimulant effect of MARINOL® (Dronabinol) Capsules in the treatment of AIDS-related anorexia associated with weight loss was studied in a randomized, double-blind, placebo-controlled study involving 139 patients. The initial dosage of MARINOL® Capsules in all patients was 5 mg/day, administered in doses of 2.5 mg one hour before lunch and one hour before supper. In pilot studies, early morning administration of MARINOL® Capsules appeared to have been associated with an increased frequency of adverse experiences, as compared to dosing later in the day. The effect of MARINOL® Capsules on appetite, weight, mood, and nausea was measured at scheduled intervals during the six-week treatment period. Side effects (feeling high, dizziness, confusion, somnolence) occurred in 13 of 72 patients (18%) at this dosage level and the dosage was reduced to 2.5 mg/day, administered as a single dose at supper or bedtime.

As compared to placebo, MARINOL® Capsules treatment resulted in a statistically significant improvement in appetite as measured by visual analog scale (see figure). Trends toward improved body weight and mood, and decreases in nausea were also seen.

After completing the 6-week study, patients were allowed to continue treatment with MARINOL® Capsules in an open-label study, in which there was a sustained improvement in appetite.



Antiemetic: MARINOL® (Dronabinol) Capsules treatment of chemotherapy-induced emesis was evaluated in 454 patients with cancer, who received a total of 750 courses of treatment of various malignancies. The antiemetic efficacy of MARINOL® Capsules was greatest in patients receiving cytotoxic therapy with MOPP for Hodgkin's and non-Hodgkin's lymphomas. MARINOL® Capsules dosages ranged from 2.5 mg/day to 40 mg/day, administered in equally divided doses every four to six hours (four times daily). As indicated in the following table, escalating the MARINOL® Capsules dose above 7 mg/m^2 increased the frequency of adverse experiences, with no additional antiemetic benefit.

MARINOL® Capsules Dose: Response Frequency and Adverse Experiences*
(N = 750 treatment courses)

MARINOL® Capsules Dose	**Response Frequency (%)**			**Adverse Events Frequency (%)**		
	Complete	Partial	Poor	None	Nondysphoric	Dysphoric
<7 mg/m^2	36	32	32	23	65	12
>7 mg/m^2	33	31	36	13	58	28

*Nondysphoric events consisted of drowsiness, tachycardia, etc.

Combination antiemetic therapy with MARINOL® Capsules and a phenothiazine (prochlorperazine) may result in synergistic or additive antiemetic effects and attenuate the toxicities associated with each of the agents.

INDIVIDUALIZATION OF DOSAGES

The pharmacologic effects of MARINOL® (Dronabinol) Capsules are dose-related and subject to considerable interpatient variability. Therefore, dosage individualization is critical in achieving the maximum benefit of MARINOL® Capsules treatment.

Appetite Stimulation: In the clinical trials, the majority of patients were treated with 5 mg/day MARINOL® Capsules, although the dosages ranged from 2.5 to 20 mg/day. For an adult:

1. Begin with 2.5 mg before lunch and 2.5 mg before supper. If CNS symptoms (feeling high, dizziness, confusion, somnolence) do occur, they usually resolve in 1 to 3 days with continued dosage.

2. If CNS symptoms are severe or persistent, reduce the dose to 2.5 mg before supper. If symptoms continue to be a problem, taking the single dose in the evening or at bedtime may reduce their severity.

3. When adverse effects are absent or minimal and further therapeutic effect is desired, increase the dose to 2.5 mg before lunch and 5 mg before supper or 5 and 5 mg. Although most patients respond to 2.5 mg twice daily, 10 mg twice daily has been tolerated in about half of the patients in appetite stimulation studies.

The pharmacologic effects of MARINOL® Capsules are reversible upon treatment cessation.

Antiemetic: Most patients respond to 5 mg three or four times daily. Dosage may be escalated during a chemotherapy cycle or at subsequent cycles, based upon initial results. Therapy should be initiated at the lowest recommended dosage and titrated to clinical response. Administration of MARINOL® Capsules with phenothiazines, such as prochlorperazine, has resulted in improved efficacy as compared to either drug alone, without additional toxicity.

Pediatrics: MARINOL® Capsules is not recommended for AIDS-related anorexia in pediatric patients because it has not been studied in this population. The pediatric dosage for the treatment of chemotherapy-induced emesis is the same as in adults. Caution is recommended in prescribing MARINOL® Capsules for children because of the psychoactive effects.

Geriatrics: Caution is advised in prescribing MARINOL® Capsules in elderly patients because they are generally more sensitive to the psychoactive effects of drugs. In antiemetic studies, no difference in tolerance or efficacy was apparent in patients >55 years old.

INDICATIONS AND USAGE

MARINOL® (Dronabinol) Capsules is indicated for the treatment of:

1. anorexia associated with weight loss in patients with AIDS; and

2. nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

CONTRAINDICATIONS

MARINOL® (Dronabinol) Capsules is contraindicated in any patient who has a history of hypersensitivity to any cannabinoid or sesame oil.

WARNINGS

Patients receiving treatment with MARINOL® Capsules should be specifically warned not to drive, operate machinery, or engage in any hazardous activity until it is established that they are able to tolerate the drug and to perform such tasks safely.

PRECAUTIONS

General: The risk/benefit ratio of MARINOL® (Dronabinol) Capsules use should be carefully evaluated in patients with the following medical conditions because of individual variation in response and tolerance to the effects of MARINOL® Capsules.

MARINOL® Capsules should be used with caution in patients with cardiac disorders because of occasional hypotension, possible hypertension, syncope, or tachycardia (see **CLINICAL PHARMACOLOGY**).

MARINOL® Capsules should be used with caution in patients with a history of substance abuse, including alcohol abuse or dependence, because they may be more prone to abuse MARINOL® Capsules as well. Multiple substance abuse is common and marijuana, which contains the same active compound, is a frequently abused substance.

MARINOL® Capsules should be used with caution and careful psychiatric monitoring in patients with mania, depression, or schizophrenia because MARINOL® Capsules may exacerbate these illnesses.

MARINOL® Capsules should be used with caution in patients receiving concomitant therapy with sedatives, hypnotics or other psychoactive drugs because of the potential for additive or synergistic CNS effects.

MARINOL® Capsules should be used with caution in pregnant patients, nursing mothers, or pediatric patients because it has not been studied in these patient populations.

Information for Patients: Patients receiving treatment with MARINOL® (Dronabinol) Capsules should be alerted to the potential for additive central nervous system depression if MARINOL® Capsules is used concomitantly with alcohol or other CNS depressants such as benzodiazepines and barbiturates.

Patients receiving treatment with MARINOL® Capsules should be specifically warned not to drive, operate machinery, or engage in any hazardous activity until it is established that they are able to tolerate the drug and to perform such tasks safely.

Patients using MARINOL® Capsules should be advised of possible changes in mood and other adverse behavioral effects of the drug so as to avoid panic in the event of such manifestations. Patients should remain under the supervision of a responsible adult during initial use of MARINOL® Capsules and following dosage adjustments.

Drug Interactions: In studies involving patients with AIDS and/or cancer, MARINOL® (Dronabinol) Capsules has been co-administered with a variety of medications (e.g., cytotoxic agents, anti-infective agents, sedatives, or opioid analgesics) without resulting in any clinically significant drug/drug interactions. Although no drug/drug interactions were discovered during the clinical trials of MARINOL® Capsules, cannabinoids may interact with other medications through both metabolic and pharmacodynamic mechanisms. Dronabinol is highly protein bound to plasma proteins, and therefore, might displace other protein-bound drugs. Although this displacement has not been confirmed *in vivo*, practitioners should monitor patients for a change in dosage requirements when administering dronabinol to patients receiving other highly protein-bound drugs. Published reports of drug/drug interactions involving cannabinoids are summarized in the following table.

CONCOMITANT DRUG	CLINICAL EFFECT(S)
Amphetamines, cocaine, other sympathomimetic agents	Additive hypertension, tachycardia, possibly cardiotoxicity
Atropine, scopolamine, antihistamines, other anticholinergic agents	Additive or super-additive tachycardia, drowsiness
Amitriptyline, amoxapine, desipramine, other tricyclic antidepressants	Additive tachycardia, hypertension, drowsiness
Barbiturates, benzodiazepines, ethanol, lithium, opioids, buspirone, antihistamines, muscle relaxants, other CNS depressants	Additive drowsiness and CNS depression
Disulfiram	A reversible hypomanic reaction was reported in a 28 y/o man who smoked marijuana; confirmed by dechallenge and rechallenge
Fluoxetine	A 21 y/o female with depression and bulimia receiving 20 mg/day fluoxetine X 4 wks became hypomanic after smoking marijuana; symptoms resolved after 4 days
Antipyrine, barbiturates	Decreased clearance of these agents, presumably via competitive inhibition of metabolism
Theophylline	Increased theophylline metabolism reported with smoking of marijuana; effect similar to that following smoking tobacco

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies in mice and rats have been conducted under the US National Toxicology Program (NTP). In the 2-year carcinogenicity study in rats, there was no evidence of carcinogenicity at doses up to 50 mg/kg/day, about 20 times the maximum recommended human dose on a body surface area basis. In the 2-year carcinogenicity study in mice, treatment with dronabinol at 125 mg/kg/day, about 25 times the maximum recommended human dose on a body surface area basis, produced thyroid follicular cell adenoma in both male and female mice but not at 250 or 500 mg/kg/day.

Dronabinol was not genotoxic in the Ames tests, the *in vitro* chromosomal aberration test in Chinese hamster ovary cells, and the *in vivo* mouse micronucleus test. It, however, produced a weak positive response in a sister chromatid exchange test in Chinese hamster ovary cells.

In a long-term study (77 days) in rats, oral administration of dronabinol at doses of 30 to 150 mg/m^2, equivalent to 0.3 to 1.5 times maximum recommended human dose (MRHD) of 90 mg/m^2/day in cancer patients or 2 to 10 times MRHD of 15 mg/m^2/day in AIDS patients, reduced ventral prostate, seminal vesicle and epididymal weights and caused a decrease in seminal fluid volume. Decreases in spermatogenesis, number of developing germ cells, and number of Leydig cells in the testis were also observed. However, sperm count, mating success and testosterone levels were not affected. The significance of these animal findings in humans is not known.

Pregnancy: Pregnancy Category C. Reproduction studies with dronabinol have been performed in mice at 15 to 450 mg/m^2, equivalent to 0.2 to 5 times maximum recommended human dose (MRHD)

of 90 mg/m^2/day in cancer patients or 1 to 30 times MRHD of 15 mg/m^2/day in AIDS patients, and in rats at 74 to 295 mg/m^2 (equivalent to 0.8 to 3 times MRHD of 90 mg/m^2 in cancer patients or 5 to 20 times MRHD of 15 mg/m^2/day in AIDS patients). These studies have revealed no evidence of teratogenicity due to dronabinol. At these dosages in mice and rats, dronabinol decreased maternal weight gain and number of viable pups and increased fetal mortality and early resorptions. Such effects were dose dependent and less apparent at lower doses which produced less maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Dronabinol should be used only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Use of MARINOL® Capsules is not recommended in nursing mothers since, in addition to the secretion of HIV virus in breast milk, dronabinol is concentrated in and secreted in human breast milk and is absorbed by the nursing baby.

Geriatric Use: Clinical studies of MARINOL® (Dronabinol) Capsules in AIDS and cancer patients did not include the sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, increased sensitivity to psychoactive effects and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adverse experiences information summarized in the tables below was derived from well-controlled clinical trials conducted in the US and US territories involving 474 patients exposed to MARINOL® (Dronabinol) Capsules. Studies of AIDS-related weight loss included 157 patients receiving dronabinol at a dose of 2.5 mg twice daily and 67 receiving placebo. Studies of different durations were combined by considering the first occurrence of events during the first 28 days. Studies of nausea and vomiting related to cancer chemotherapy included 317 patients receiving dronabinol and 68 receiving placebo.

A cannabinoid dose-related "high" (easy laughing, elation and heightened awareness) has been reported by patients receiving MARINOL® Capsules in both the antiemetic (24%) and the lower dose appetite stimulant clinical trials (8%) (see **Clinical Trials**).

The most frequently reported adverse experiences in patients with AIDS during placebo-controlled clinical trials involved the CNS and were reported by 33% of patients receiving MARINOL® Capsules. About 25% of patients reported a minor CNS adverse event during the first 2 weeks and about 4% reported such an event each week for the next 6 weeks thereafter.

PROBABLY CAUSALLY RELATED: Incidence greater than 1%.
Rates derived from clinical trials in AIDS-related anorexia (N=157) and chemotherapy-related nausea (N=317). Rates were generally higher in the anti-emetic use (given in parentheses).

Body as a whole: Asthenia.
Cardiovascular: Palpitations, tachycardia, vasodilation/facial flush.
Digestive: Abdominal pain*, nausea*, vomiting*.
Nervous system: (Amnesia), anxiety/nervousness, (ataxia), confusion, depersonalization, dizziness*, euphoria*, (hallucination), paranoid reaction*, somnolence*, thinking abnormal*.

*Incidence of events 3% to 10%

PROBABLY CAUSALLY RELATED: Incidence less than 1%.
Event rates derived from clinical trials in AIDS-related anorexia (N=157) and chemotherapy-related nausea (N=317).

Cardiovascular: Conjunctivitis*, hypotension*.
Digestive: Diarrhea*, fecal incontinence.
Musculoskeletal: Myalgias.
Nervous system: Depression, nightmares, speech difficulties, tinnitus.
Skin and Appendages: Flushing*.
Special senses: Vision difficulties.

*Incidence of events 0.3% to 1%

CAUSAL RELATIONSHIP UNKNOWN: Incidence less than 1%.
The clinical significance of the association of these events with MARINOL® Capsules treatment is unknown, but they are reported as alerting information for the clinician.

Body as a whole: Chills, headache, malaise.
Digestive: Anorexia, hepatic enzyme elevation.
Respiratory: Cough, rhinitis, sinusitis.
Skin and Appendages: Sweating.

DRUG ABUSE AND DEPENDENCE

MARINOL® (Dronabinol) Capsules is one of the psychoactive compounds present in cannabis, and is abusable and controlled [Schedule III (CIII)] under the Controlled Substances Act. Both psychological and physiological dependence have been noted in healthy individuals receiving dronabinol, but addiction is uncommon and has only been seen after prolonged high dose administration.

Chronic abuse of cannabis has been associated with decrements in motivation, cognition, judgement, and perception. The etiology of these impairments is unknown, but may be associated with the complex process of addiction rather than an isolated effect of the drug. No such decrements in psychological, social or neurological status have been associated with the administration of MARINOL® Capsules for therapeutic purposes.

In an open-label study in patients with AIDS who received MARINOL® Capsules for up to five months, no abuse, diversion or systematic change in personality or social functioning were observed despite the inclusion of a substantial number of patients with a past history of drug abuse.

An abstinence syndrome has been reported after the abrupt discontinuation of dronabinol in volunteers receiving dosages of 210 mg/day for 12 to 16 consecutive days. Within 12 hours after discontinuation, these volunteers manifested symptoms such as irritability, insomnia, and restlessness. By approximately 24 hours post-dronabinol discontinuation, withdrawal symptoms intensified to include "hot flashes", sweating, rhinorrhea, loose stools, hiccoughs and anorexia.

These withdrawal symptoms gradually dissipated over the next 48 hours. Electroencephalographic changes consistent with the effects of drug withdrawal (hyperexcitation) were recorded in patients after abrupt dechallenge. Patients also complained of disturbed sleep for several weeks after discontinuing therapy with high dosages of dronabinol.

OVERDOSAGE

Signs and symptoms following MILD MARINOL® (Dronabinol) Capsules intoxication include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth and tachycardia; following MODERATE intoxication include memory impairment, depersonalization, mood alteration, urinary retention, and reduced bowel motility; and following SEVERE intoxication include decreased motor coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients may experience panic reactions and seizures may occur in patients with existing seizure disorders.

The estimated lethal human dose of intravenous dronabinol is 30 mg/kg (2100 mg/ 70 kg). Significant CNS symptoms in antiemetic studies followed oral doses of 0.4 mg/kg (28 mg/70 kg) of MARINOL® Capsules.

Management: A potentially serious oral ingestion, if recent, should be managed with gut decontamination. In unconscious patients with a secure airway, instill activated charcoal (30 to 100 g in adults, 1 to 2 g/kg in infants) via a nasogastric tube. A saline cathartic or sorbitol may be added to the first dose of activated charcoal. Patients experiencing depressive, hallucinatory or psychotic reactions should be placed in a quiet area and offered reassurance. Benzodiazepines (5 to 10 mg diazepam *po*) may be used for treatment of extreme agitation. Hypotension usually responds to Trendelenburg position and IV fluids. Pressors are rarely required.

DOSAGE AND ADMINISTRATION

Appetite Stimulation: Initially, 2.5 mg MARINOL® (Dronabinol) Capsules should be administered orally twice daily (b.i.d.), before lunch and supper. For patients unable to tolerate this 5 mg/day dosage of MARINOL® Capsules, the dosage can be reduced to 2.5 mg/day, administered as a single dose in the evening or at bedtime. If clinically indicated and in the absence of significant adverse effects, the dosage may be gradually increased to a maximum of 20 mg/day MARINOL® Capsules, administered in divided oral doses. Caution should be exercised in escalating the dosage of MARINOL® Capsules because of the increased frequency of dose-related adverse experiences at higher dosages (see **PRECAUTIONS**).

Antiemetic: MARINOL® Capsules is best administered at an initial dose of 5 mg/m^2, given 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy is given, for a total of 4 to 6 doses/day. Should the 5 mg/m^2 dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/m^2 increments to a maximum of 15 mg/m^2 per dose. Caution should be exercised in dose escalation, however, as the incidence of disturbing psychiatric symptoms increases significantly at maximum dose (see **PRECAUTIONS**).

STORAGE CONDITIONS

MARINOL® (Dronabinol) Capsules should be packaged in a well-closed container and stored in a cool environment between 8° and 15°C (46° and 59°F) and alternatively could be stored in a refrigerator. Protect from freezing.

HOW SUPPLIED

MARINOL® Capsules (dronabinol solution in sesame oil in soft gelatin capsules)

2.5 mg white capsules (Identified UM or RL).

NDC 0051-0021-21 (Bottle of 60 capsules).

5 mg dark brown capsules (Identified UM or RL).
NDC 0051-0022-11 (Bottle of 25 capsules).

10 mg orange capsules (Identified UM or RL).
NDC 0051-0023-21 (Bottle of 60 capsules).

MARINOL® is a registered trademark of Unimed Pharmaceuticals, Inc. and is
Manufactured by Banner Pharmacaps, Inc.
High Point, NC 27265

500012 Rev Sep 2004

A Solvay Pharmaceuticals, Inc. Company
Marietta, GA 30062

Sue Sisley, MD

Sue Sisley, M.D.

Dr. Sue Sisley MD is an Arizona-based physician practicing Internal Medicine and Psychiatry. She works as Medical Director for medical cannabis license holders in 11 different states from Hawaii to Puerto Rico to New York. Dr. Sisley serves as Site Principal Investigator for the only FDA-approved randomized controlled trial in the world examining safety/efficacy of whole plant marijuana in combat veterans with treatment-resistant post traumatic stress disorder PTSD.

Dr. Sisley is on faculty at Colorado State University, recruited for core planning team to organize the CSU "Cannabis Center of Excellence" in Pueblo, Colorado. Dr. Sisley has been a Member of Nevada ILAC Medical Cannabis Commission for the past two years outlining regulations for laboratory testing including limits on pesticides, residual solvents and other guidelines that are currently being used as a model for other states medical cannabis laws.

Efficacy of Cannabis for Treatment of Medical Conditions

Sue Sisley, MD

January 11, 2017

Cannabis Efficacy: Where Are We Now?

- Solid clinical trial proof for cannabinoid therapy exists for cannabis, THC and CB_1 agonists:

  Nausea and vomiting

  Anorexia associated with chemotherapy, HIV/AIDS

  Spasticity in multiple sclerosis and other neurological conditions

  Neuropathic pain, whether peripheral or central

  Cancer pain

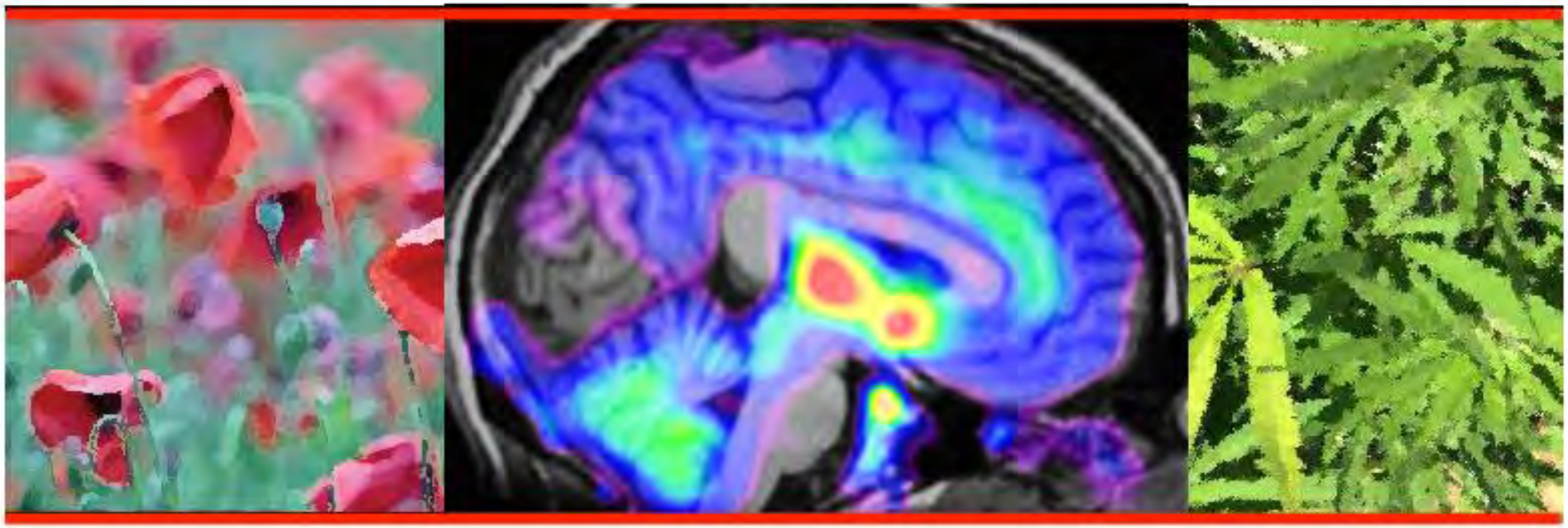
  Lower urinary tract symptoms (LUTS)

- For cannabidiol (CBD):

  Intractable epilepsy

  Schizophrenia, positive and negative symptoms

Opioids and Cannabis: Myths and Misperceptions



Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse
@NIDAnews

Improving Treatments for Pain:

Safer Analgesics

Opioid deterrent formulations

Pro-drugs

Tamper resistant formulation

Drug combinations with adverse effects if injected

Non-Opioid based analgesics

Cannabinoids;
Inflammatory mediators;
Ion channel blockers

Non-pharmacological mechanisms and treatments

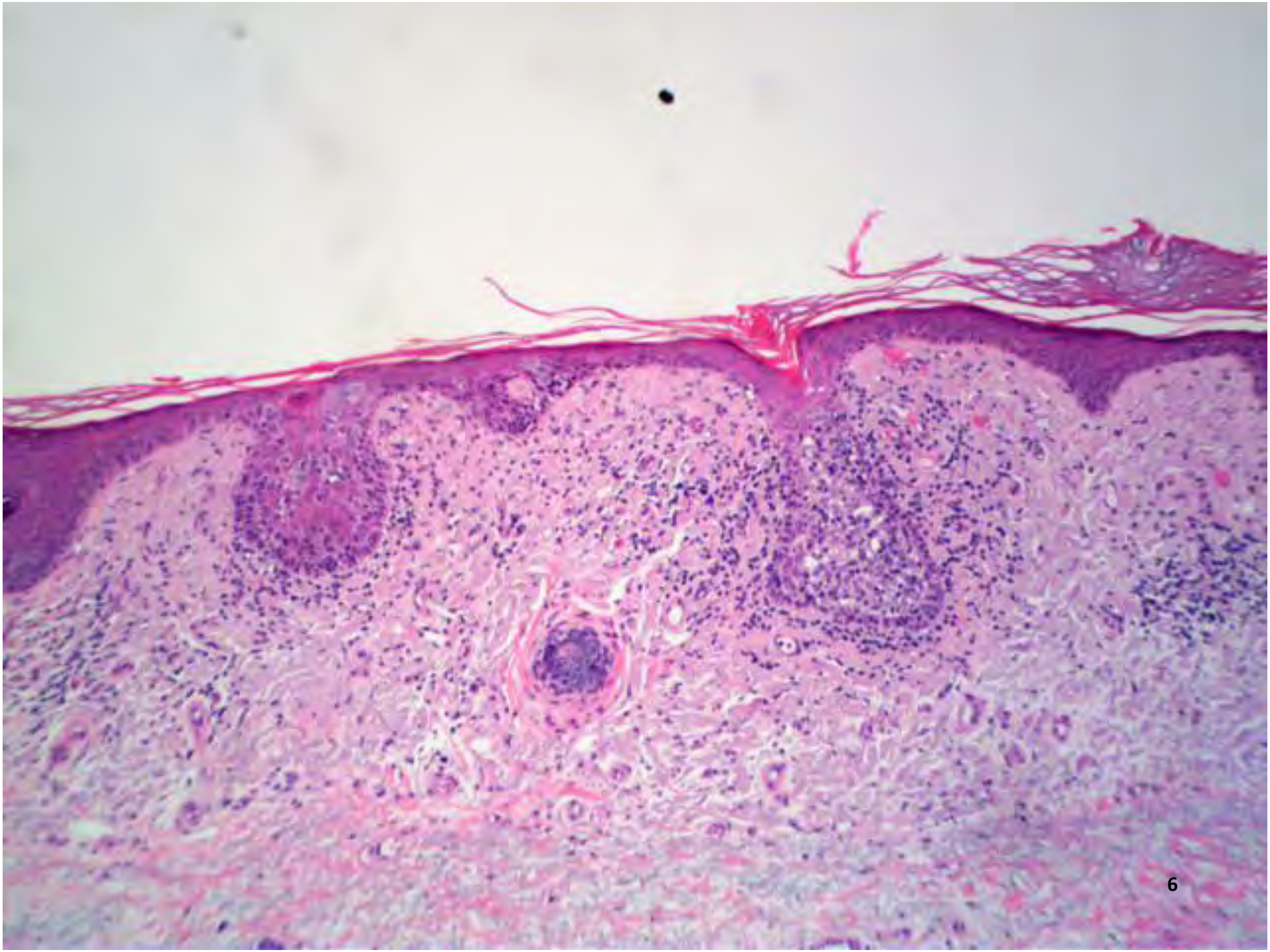
Surgical interventions for pain;
Neural stimulation technologies for chronic pain; Spinal cord stimulation

PTSD Symptom Reports of Patients Evaluated for the New Mexico Medical Cannabis Program

George R. Greer M.D., Charles S. Grob M.D. & Adam L. Halberstadt Ph.D. (2014) PTSD Symptom Reports of Patients Evaluated for the New Mexico Medical Cannabis Program, ***Journal of Psychoactive Drugs,*** 46:1, 73-77, DOI:

- The purpose of the study was to report and statistically analyze PTSD symptoms collected during 80 psychiatric evaluations of patients applying to the New Mexico Medical Cannabis Program from 2009 to 2011.

- Greater than 75% reduction in CAPS symptom scores were reported when patients were using cannabis compared to when they were not



Abrams DI, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology.* 2007;68(7):515-21.

- Smoked NIDA cannabis in 50 subjects TID for **5 days**
- Results
  - decreased daily pain (p=0.03)
- **AEs in smoking group (psychoactive effects) were prominent**

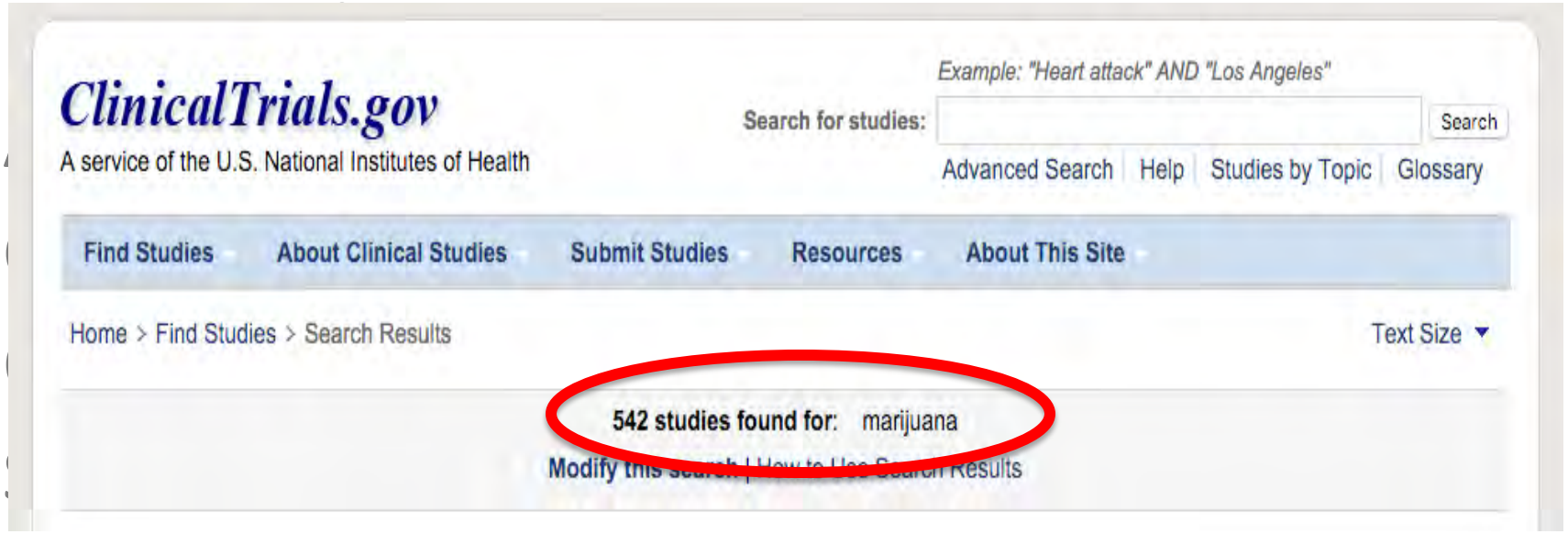
	Adjusted estimates	
	Cannabis, mean (95% CI)	Placebo, mean (95% CI)
Anxiety*	0.25 (0.14, 0.44)	0.10 (0.05, 0.22)
Sedation†	0.54 (0.36, 0.81)	0.08 (0.04, 0.17)
Disorientation†	0.16 (0.07, 0.34)	0.01 (0.00, 0.04)
Paranoia	0.13 (0.03, 0.45)	0.04 (0.01, 0.14)
Confusion†	0.17 (0.07, 0.39)	0.01 (0.00, 0.06)
Dizziness†	0.15 (0.07, 0.31)	0.02 (0.01, 0.05)
Nausea	0.11 (0.04, 0.30)	0.03 (0.01, 0.14)

Side effects were rated three times daily on a 0 to 3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

* p, 0.05; † $p < 0.001$.

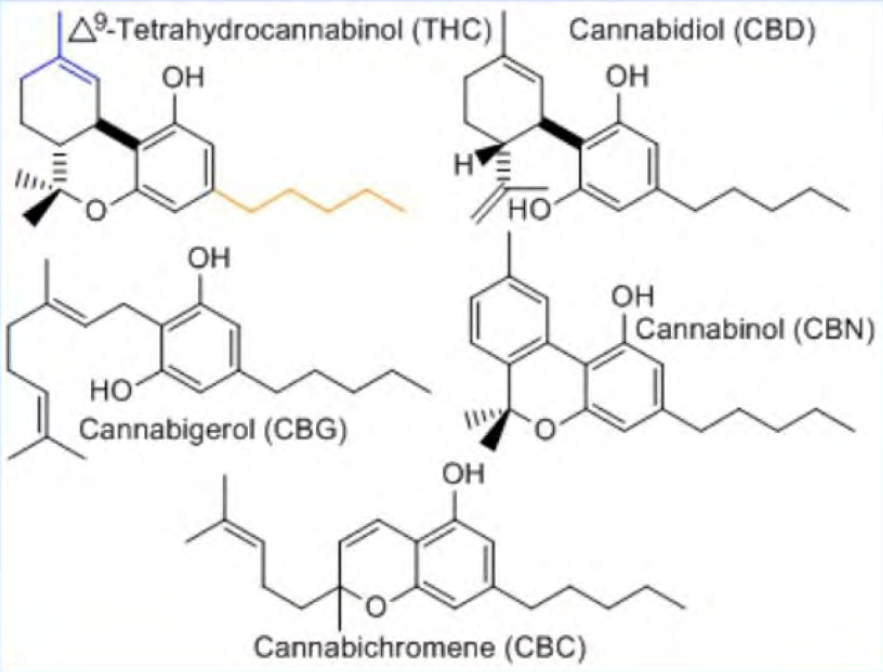
- S
- A
- F
- A

ADHS Medical Marijuana Program



Advises patients of trials

Various cannabinoids, principally THC and CBD, work in a complex relationship across various targets producing an "entourage effect"

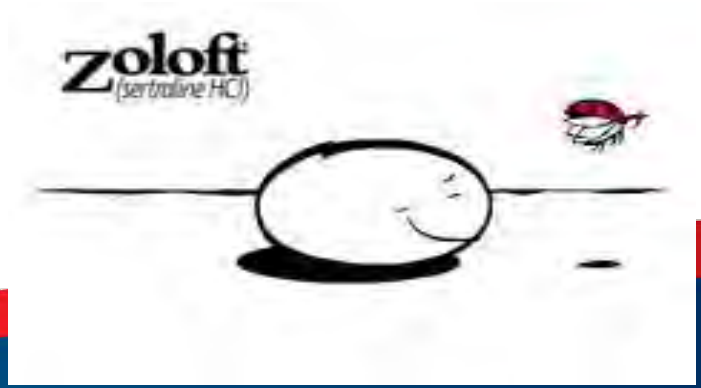


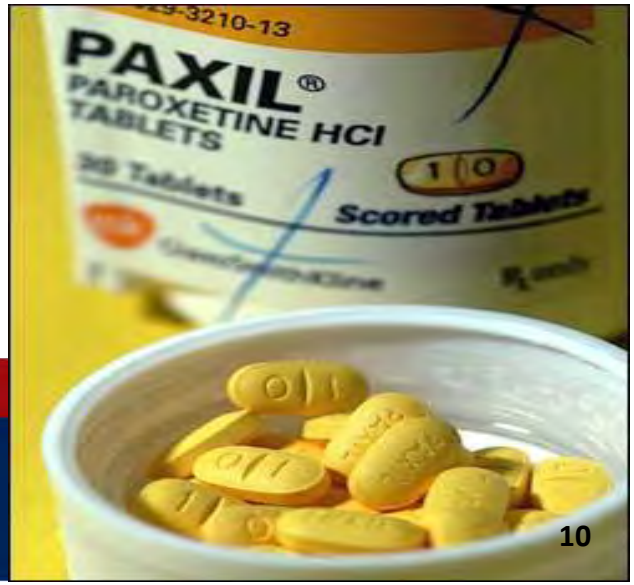
For instance, CBD competes with THC at CB1 receptor, possibly decreasing anxiety often associated with THC-only medicines

For this reason, **whole-plant** use makes more sense than isolated individual cannabinoids

Why Study New Treatments for PTSD?

A significant percentage of PTSD patients fail to respond adequately to FDA-approved treatments, suggesting a need to develop INNOVATIVE treatments





FDA PTSD Study Timeline

- November 12, 2010
  - Protocol submitted to the FDA
- Morning April 28, 2011
  - Protocol approved by FDA; sent to DEA/NIDA
- OVER 5 YEARS to finally obtain approval from DEA/NIDA

FDA PTSD Study: Phase 2 Objectives

- To investigate the safety/efficacy of 4 different strains of marijuana
- (0% PLACEBO, 12% CBD, 12% THC or 12% THC/12% CBD),

To treat veterans with chronic, treatment-resistant, combat-related PTSD

- DELIVERY METHOD approved by FDA: SMOKING

NIDA Monopoly

- The National Institute of Drug Abuse holds a government-enforced monopoly on the ONLY legal supply of research marijuana.

- Marijuana is the only Schedule 1 drug for which the federal government not only controls the research supply, but also requires a special review of all scientific protocols by a NIDA/Public Health Service (PHS) review panel.

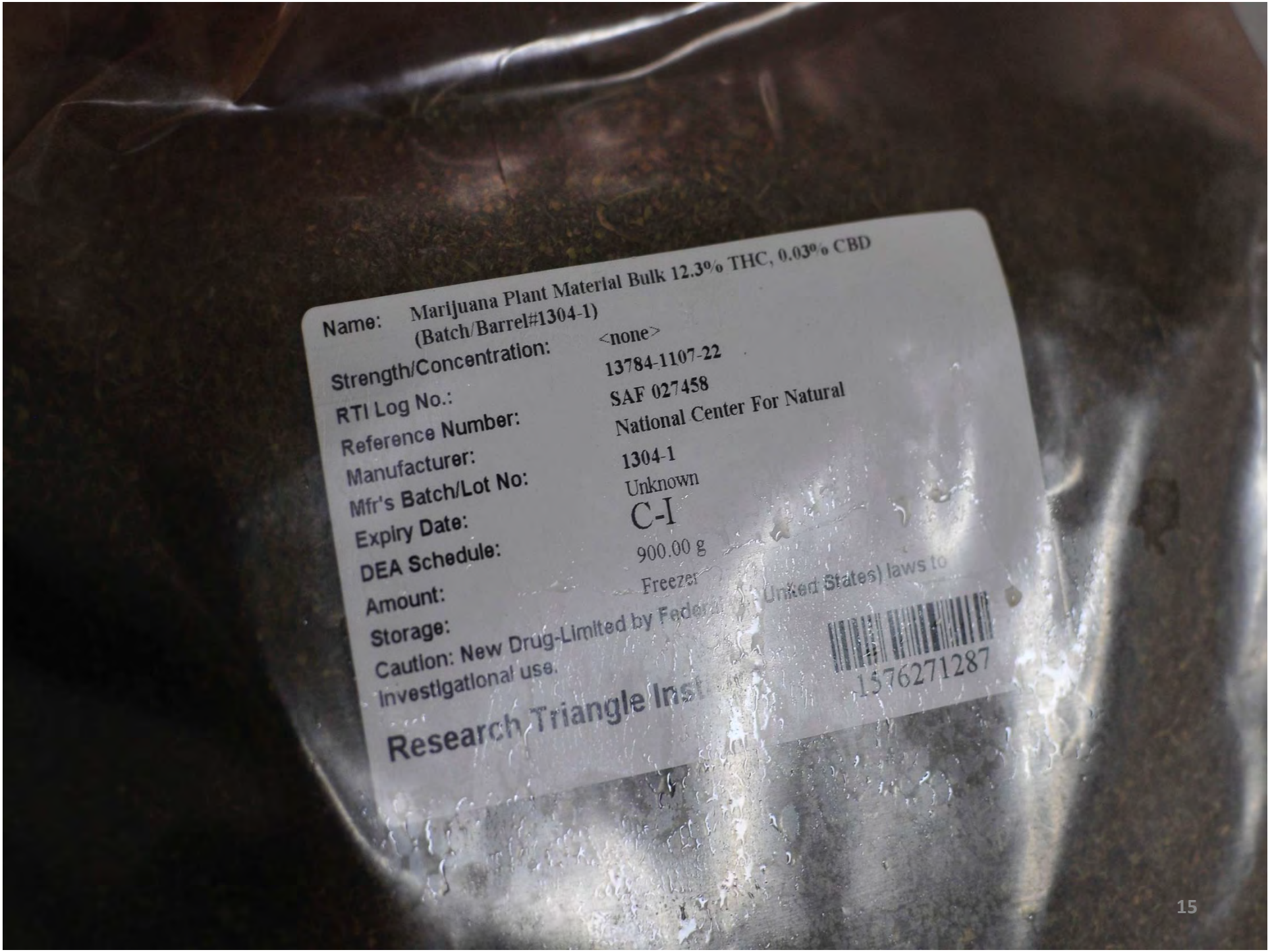
NIDA NATIONAL INSTITUTE ON DRUG ABUSE
The Science of Drug Abuse & Addiction
NATIONAL INSTITUTES OF HEALTH

?

NIDA Monopoly

- Since 1968 DEA has licensed only 1 Cannabis-production facility in the US, housed @ University of Mississippi

- If NIDA decides not to sell Cannabis to a group of researchers, their study becomes impossible to conduct.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Strength/Concentration: <none>
RTI Log No.: 13784-1107-22
Reference Number: SAF 027458
Manufacturer: National Center For Natural
Mfr's Batch/Lot No: 1304-1
Expiry Date: Unknown
DEA Schedule: C-I
Amount: 900.00 g
Storage: Freezer
Caution: New Drug-Limited by Fede
United States) laws to
investigational use.
Research Triangle Inst
1576271287


Are you a U.S. Military Veteran?
Have you experienced traumatic stress?
Adult military veterans who experienced trauma while in military service are needed for a research study. Study volunteers will complete 17 outpatient study visits over 12 weeks and a 6-month follow-up visit.
The study will evaluate the effects of an investigational drug, cannabis. Eligibility is determined by medical evaluations and modest compensation for participation is provided.
All study visits occur at the SCOTTSDALE RESEARCH INSTITUTE
For more information email arizona@marijuanasites.org

THANK YOU

(for attention + partnership)

Questions?

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